Optimisation of Neonatal Ventilation

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Optimisation of Neonatal Ventilation

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Abstract

Background: Survival of neonates requiring intensive care has improved, but many suffer ventilator-related complications. This thesis aims to optimise use of ventilation techniques, with a focus on infants born at term.

Hypotheses:

- In infants with acute respiratory failure, volume-targeted ventilation (VTV) will be superior to pressure-limited ventilation (PLV).
- Proportional assist ventilation (PAV) will be effective in reducing elastic and resistive work of breathing (WOB) in an *in vitro* experiment.

Methods: A series of studies were undertaken.

- National survey of practice in relation to respiratory support in term infants
- Comparison of WOB at different levels of volume-targeting in term infants
- Randomised comparison of VTV and PLV in preterm infants
- Analysis of spontaneous respiratory activity in ventilated term infants
- *In vitro* study of effect of elastic and resistive unloading on WOB during PAV

Results: Respiratory support practices for term-born infants differed between different levels of care. In term infants, WOB was higher at 4ml/kg compared to 5 and 6ml/kg. In preterm infants, there was no difference in time to achieve weaning criteria on VTV versus PLV. Fewer infants on VTV experienced hypocarbia. Patterns of patient-ventilator interaction were described for term-born infants. Active expiration was more common on SIMV versus CMV, and less common on triggered ventilation at 4ml/kg compared to 6ml/kg or no volume-targeting. Using PAV, elastic unloading was more effective than resistive unloading in reducing WOB.

Declaration

The statistical analysis for the RCT described in Chapter 5 was carried out by Professor Janet Peacock; I thank her for her assistance in this regard. Dr Catherine Wedderburn provided assistance with the survey described in Chapter 3 – she consolidated the database of contacts for the UK neonatal units and helped with administration of the electronic survey. Otherwise, all the work described in this thesis is my own.

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Publications arising from this thesis

Chowdhury O, Bhat P, Rafferty GF, Milner AD, Greenough A. In vitro assessment of the effect of proportional assist ventilation on the work of breathing. Submitted for publication.

Chowdhury O, Patel DS, Hannam S, Lee S, Rafferty GF, Peacock JL, Greenough A. Randomised trial of volume-targeted ventilation versus pressure-limited ventilation in acute respiratory failure in prematurely born infants. Neonatology. 2013;104(4):290-4

Chowdhury O, Wedderburn CJ, Lee S, Hannam S, Greenough A. Respiratory support practices in infants born at term in the United Kingdom. Eur J Pediatr. 2012 Nov;171(11):1633-8.

Chowdhury O, Rafferty GF, Lee S, Hannam S, Milner AD, Greenough A. Volume-targeted ventilation in infants born at or near term. Arch Dis Child Fetal Neonatal Ed. 2012 Jul;97(4):F264-6.

Abbreviations used in this thesis

ACV	Assist/Control Ventilation
ARDS	Adult Respiratory Distress Syndrome
BAL	Bronchoalveolar Lavage
BAPM	British Association of Perinatal Medicine
BLISS	Baby Life Support Systems
BPD	Bronchopulmonary Dysplasia
CDH	Congenital Diaphragmatic Hernia
CI	Confidence Interval
cm	centimetres
CMACE	Centre for Maternal and Child Enquiries
CMV	Continuous Mandatory Ventilation
CPAP	Continuous Positive Airway Pressure
CV	Conventional Ventilation
ECMO	Extracorporeal Membrane Oxygenation
Edi	Electrical activity of the diaphragm
EIT	Electrical Impedance Tomography
ET	Endotracheal
FEV_1	Forced expiratory volume in 1 second
FiO_2	Fraction of inspired oxygen
g	gram
GI	Gastrointestinal
H_2O	Water
HFOV	High Frequency Oscillatory Ventilation
HIE	Hypoxic Ischaemic Encephalopathy
hr	hour(s)
Hz	Hertz

IL-8	Interleukin 8
IMV	Intermittent Mandatory Ventilation
IPPV	Intermittent Positive Pressure Ventilation
IVH	Intraventricular Haemorrhage
kg	kilogram
kPa	kilopascal
L	Litre
LNU	Local Neonatal Unit
MAP	Mean Airway Pressure
MAS	Meconium Aspiration Syndrome
MD	Mean Difference
min	minute
MIP-2	Macrophage Inflammatory Protein 2
ml	millilitres
NAVA	Neurally Adjusted Ventilatory Assist
NHS	National Health Service
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NO	Nitric oxide
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PAV	Proportional Assist Ventilation
P_{aw}	Airway pressure
PDA	Patent Ductus Arteriosus
P_{di}	Transdiaphragmatic pressure
PEEP	Positive End-Expiratory Pressure
Pemax	maximal expiratory pressure
P_{gas}	Gastric pressure

pH	power of hydrogen
PICU	Paediatric Intensive Care Unit
Pimax	maximal inspiratory pressure
PIP	Peak Inflation Pressure
PLV	Pressure-limited ventilation
PMA	Postmenstrual age
P_{oes}	Oesophageal pressure
PPHN	Persistent Pulmonary Hypertension of the Newborn
P_{pl}	Pleural pressure
ppm	parts per million
PRVC	Pressure-Regulated Volume Control
PSV	Pressure Support Ventilation
PTP_{di}	Transdiaphragmatic Pressure-Time Product
PVL	Periventricular leukomalacia
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
RR	Respiratory rate
RR	Risk Ratio
s	second(s)
SCU	Special Care Unit
SD	Standard Deviation
sec	second(s)
SIMV	Synchronised Intermittent Mandatory Ventilation
SIPPV	Synchronised Intermittent Positive Pressure Ventilation
T_i	Inflation Time
T_r	Response Time
TTN	Transient Tachypnea of the Newborn
TTV^{plus}	Targeted Tidal Volume plus

USA	United States of America
VALI	Ventilator-Associated Lung Injury
VAPS	Volume-Assured Pressure Support
VG	Volume Guarantee
VIDD	Ventilator-Induced Diaphragmatic Dysfunction
VILI	Ventilator-Induced Lung Injury
VLBW	Very Low Birth Weight
VT	Volume target
VT_e	Expiratory tidal volume
VTV	Volume-targeted ventilation
WOB	Work of breathing

Chapter 1: Introduction

1.1 Background

1.1.1 Historical perspective

Mechanical ventilation of neonates has been described since the eighteenth century. Gorcy, a French physician, developed a bellows-to-tube design of ventilator (1), which could provide intermittent positive pressure breaths to infant lungs using atmospheric air. In 1828, concerns were raised that artificial ventilation caused pneumothoraces (2). In 1829, Magendie and Dumeril were commissioned by the French Academy of Sciences to investigate the findings of the Parisian surgeon Leroy, who opined that distension of the chest with artificial insufflation of air was perhaps harmful in comparison to natural respirations (2). The commission published their findings (3) confirming that uncontrolled insufflations of air into the trachea could cause sudden death, recommending that this technique should only be used if applied gently in experienced hands. Following this, interest in intermittent positive pressure ventilation waned and did not gain momentum again until the twentieth century. For the most part of the twentieth century, neonatal ventilators were modified versions of adult ones. An increasing understanding of neonatal respiratory insufficiency helped develop techniques of neonatal ventilation. In 1953, Donald and Lord published a detailed report of their experience of ventilation in ‘atelectasis neonatorum’ (4). They described the difficulties faced using a Drinker type of apparatus which was a crank-operated bellows-type ventilator which enabled delivery of positive pressure ventilation at different rates and pressures. Disappointing results using this type of ventilator were attributed to asynchrony leading to

ineffective ventilation and hyperventilation resulting in alkalotic tetany. The authors attempted to overcome these issues by use of a ‘servo patient-cycled respirator’. They described an obvious need for ‘a machine which would amplify spontaneous respiratory efforts however irregular’, in what seems an almost prophetic foreshadowing of proportional assist ventilation, one of the modes investigated in this thesis. This concept was far ahead of its time. The combination of severe hyaline membrane disease and intracranial haemorrhage resulted in early fatalities (4) and servo-controlled modes of neonatal ventilation were not studied again systematically till several decades later.

1.1.2 Epidemiology of ventilated newborns

Data from 1994 for New York and California, which included 15,006 ventilated newborns, demonstrated that 17.8 per thousand livebirths without congenital anomalies required mechanical ventilation (5). In this study, only 36.7% of the ventilated infants weighed less than 1500 grams, suggesting that the majority of newborns requiring mechanical ventilation were not born extremely prematurely. Rates of mechanical ventilation per 1000 livebirths were 502.8 in those born very low birthweight (VLBW), 112.9 in low birthweight and 7.2 in normal birthweight neonates.

An epidemiological study from 2008 (6) of 65,000 newborns in France showed that the incidence of requirement of mechanical ventilation was also lower in infants born at term, but was not insubstantial, being 3.6 per 1000 live born term infants (37-41 weeks gestation) without major congenital malformations and/or chromosomal abnormalities. Data from New South Wales in Australia (7) showed

a rate of mechanical ventilation of 2.6-3.2 per 1000 live born term infants (≥ 37 weeks gestation) without major congenital anomalies for the years 1992 to 1994, an increase on the rate of 1.6 per thousand in 1987. Yet, optimisation of ventilation of term born infants has rarely been researched and, therefore, will be a major focus of this thesis.

1.1.3 Underlying respiratory disease

1.1.3.1 Term born infants

Of the term infants included in Gouyon's study (6), 56% had pulmonary pathology and the remaining were ventilated for non-respiratory illness. The most common respiratory conditions necessitating ventilation were transient tachypnoea of the newborn (TTN) (36%), meconium aspiration syndrome (MAS) (31%), respiratory distress syndrome (RDS) (19%), pulmonary infection (8%), pneumothorax (3%) and persistent pulmonary hypertension of the newborn (PPHN) (2%). Of the ventilated newborns with non-respiratory illness, 40% had severe birth asphyxia. In Sutton's study (7) of term newborns in New South Wales, the main indications for mechanical ventilation (1992 data) were asphyxia (28.6%), MAS (22.5%), RDS (21%), TTN (9.5%), PPHN (5.7%) and infection (4.2%). In contrast, in Clark's study (8) of 1011 ventilated newborns born at a gestation of 34 weeks or above the most common respiratory conditions associated with the need for ventilation were RDS (43%), MAS (10%), pneumonia/sepsis (8%), TTN (4%), primary PPHN (3%) and aspiration of blood or amniotic fluid (2%). The difference in results compared to the previous study (6) likely reflects the inclusion of infants who were born between 34 and 37 weeks gestation in Clark's study. Infants born at 34 weeks have a forty-fold increased risk of RDS than those born at term (9). Non-respiratory diagnoses leading to the need for mechanical ventilation were major

congenital anomalies (17%), severe hypoxic ischaemic encephalopathy (3%) and perioperative support (2%) (8).

1.1.3.2 Prematurely born infants

Prematurely born infants have lungs that are immature in structure and biochemical function, as well as immature respiratory drive. Lung development in the fetus occurs in distinct stages – embryonic (3rd to 7th week of gestation), pseudoglandular (7th to 16th week of gestation), canalicular (16th to 24th week of gestation), saccular (24th week of gestation to term) and alveolar (postnatal period to approximately 8 years of age). Extremely premature births occur within the late canalicular or early saccular phases of lung development. The late canalicular stage is characterised by cell differentiation to Type I and II pneumocytes, with gas exchange becoming physiologically possible by the end of this phase. Epidemiological studies (10, 11) have shown that RDS is the leading respiratory pathology affecting prematurely born infants. RDS results from surfactant deficiency. Surfactant production in the fetal lung begins during the canalicular stage of lung development during 20 to 22 weeks of gestation; sufficient levels are reached at about 35 weeks gestation. Even with significant changes in practice between the late 1990s and early 2000s, with increased administration of antenatal steroids and early administration of exogenous surfactant, infants less than 28 weeks gestation with bronchopulmonary dysplasia (BPD) in an observational study from the United States were shown to have significantly higher duration of mechanical ventilation coinciding with significantly reduced rates of postnatal steroid therapy (12).

1.1.4 Mortality

Respiratory disorders are the leading cause of neonatal death in the United Kingdom; 37.7% of neonatal deaths in 2008 and 34.4% of neonatal deaths in 2009 were attributed to respiratory disorders (13, 14). In 2009, of all neonatal deaths, severe pulmonary immaturity accounted for 20.2% of deaths, pulmonary hypoplasia for 4.1%, surfactant deficiency lung disease for 3.6%, PPHN for 0.9%, MAS for 0.8% and BPD for 0.3% (14). Other respiratory disorders accounted for the remaining 4.6% of deaths attributable to respiratory causes (14). It is not clear from the CMACE data what proportion of neonates dying of respiratory causes received mechanical ventilation.

Angus reported an overall mortality rate of 11% in ventilated neonates across all gestations (5). Gouyon and Clark reported mortality rates of 5% (6) and 6% (8) respectively in mechanically ventilated neonates born at term.

1.1.5 Morbidity

1.1.5.1 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) was first described by Northway and colleagues in 1967 (15). The original description of BPD was that of fibrotic and cystic changes in the lung, brought about by mechanical ventilation with high pressures and oxygen therapy. In the era of surfactant use and with increasingly immature infants being given intensive care, lungs of infants dying from BPD have less fibrosis, but deficient alveolarisation (16), leading to the concept that the BPD seen nowadays results from arrested lung development (17).

BPD is now usually diagnosed if an infant is dependent on oxygen and/or positive pressure ventilation at the age of 28 days (18). The severity of the BPD is

assessed at 36 weeks postmenstrual age (PMA) for infants born at less than 32 weeks gestation and between 4 to 8 weeks of life in infants born at or more than 32 weeks (Table 1.1).

Gestational Age	< 32 weeks	>32 weeks
Time of assessment	36w PMA or discharge home*	>28d but <56d postnatal age or discharge home*
Treatment with >21% oxygen for at least 28 days plus:		
Mild BPD	Breathing room air at 36w PMA or discharge home*	Breathing room air at 56 days postnatal age or discharge home*
Moderate BPD	Need for <30% oxygen at 36w PMA or discharge home*	Need for <30% oxygen at 56 days postnatal age or discharge home*
Severe BPD	Need for > 30% oxygen with or without positive pressure ventilation or CPAP at 36w PMA or discharge home*	Need for > 30% oxygen with or without positive pressure ventilation or CPAP at 56 days postnatal age or discharge home*

* Whichever comes first

Table 1.1 Diagnostic criteria for defining BPD (18).

Walsh proposed a physiologic definition of BPD (19) as a more objective measure of oxygen dependency in preterm infants. The diagnosis of BPD was determined at 36 weeks PMA by applying an oxygen reduction test. Infants receiving a fractional inspired oxygen of ≤ 0.3 or > 0.3 with saturations above 96% were administered a room-air challenge. Infants maintaining saturations ≥ 90% in room air for 30 minutes were classified as not having BPD; if saturations dropped below 90% during the challenge, a diagnosis of BPD was made. In a multicentre study, the incidence of BPD in VLBW infants was reported as 35% using the NICHD workshop definition, but only 25% using the oxygen reduction test (19), highlighting that a significant proportion of infants may have been receiving supplementary oxygen inappropriately.

BPD is associated with long-term respiratory morbidity. Differences in lung function can be detected from an early age and may persist into late adolescence. Northway followed up a group born between 1964 and 1973 and diagnosed with the 'old' BPD, at a mean age of 18 years, comparing them to matched controls who had never been ventilated and age-matched non-premature controls (20). The BPD group demonstrated airway obstruction in 68% of subjects, which was fixed in a quarter of those affected. The BPD group also had significantly worse airflow obstruction and increased gas-trapping. In an Australian study (21) of VLBW survivors from the period 1977 to 1982, studied at a mean age of 19 years, 22% of the cohort was defined as having the 'old' BPD and had significantly worse airflow obstruction but not abnormal lung volumes. Rates of asthma were similar in the BPD and control groups.

The evolution of BPD from the 'old' to the 'new', coinciding with the era of surfactant use, has possibly made some difference to long-term respiratory

outcomes. One study (22) demonstrated lower FEV_1 in the 'new' BPD group compared to both non-BPD preterm and term controls at 7-8 years of age, a finding similar to studies assessing children born in the pre-surfactant era. A much larger Australian study (23) assessing children at a mean age of 9 years, however, demonstrated that the majority of children in the 'new' BPD group had lung function within normal range. The difference in FEV_1 between BPD and non-BPD, prematurely born groups was nearly half that found from a similar study in the pre-surfactant era (21). Children with BPD have been shown to have higher rates of rehospitalisation (24, 25), multiple rehospitalisations (26) and longer stays in hospital (27) compared to those without BPD.

Large studies have indicated that incidence of BPD has not changed significantly (28, 29). A nationwide study from the USA (30) however, including data from 9.5 million VLBW infants between 1993 and 2006, showed an overall 4.3% decrease per year in the incidence of BPD in neonates who survived to discharge. Despite this reduction in BPD rates, both hospital length of stay and hospital cost of care increased significantly for neonates with BPD, with annual increases of 3.9% and 4.9% respectively, suggesting that the infants surviving with this condition are sicker.

In infants born at term, the rate of long-term oxygen dependency is less, with Gouyon reporting rates of 5% (chronic lung disease defined as receiving supplemental oxygen at 28 days of life) in infants between 37 and 41 weeks gestation who required mechanical ventilation (6) and Clark reporting rates of 11% (chronic lung disease defined as receiving supplemental oxygen at 30 days of life) in infants 34 weeks or above in gestation who were ventilated (8).

1.1.5.2 Pneumothorax

Pneumothorax is a complication of mechanical ventilation. Greenough et al demonstrated that infants displaying a pattern of active expiration against ventilator inflations were at higher risk of pneumothoraces (31). With improved ventilator technology and the routine use of prophylactic surfactant, the incidence of pneumothorax has decreased. A systematic review (32) has shown that prophylactic surfactant compared to selective surfactant was associated with a significantly reduced risk of pneumothorax (RR 0.62, 95% CI 0.42, 0.89) as well as pulmonary interstitial emphysema (RR 0.54, 95% CI 0.36, 0.82). The introduction of patient-triggered, synchronised modes of ventilation was not accompanied by a demonstrable reduction in pneumothorax. A systematic review comparing triggered modes to CMV did not show any impact of triggered modes on the incidence of air leaks in neonates (33). Volume-targeted ventilation in prematurely born infants has been shown to be associated with a lower incidence of pneumothorax in a systematic review (RR 0.46, 95% CI 0.25, 0.84) (34). Pneumothoraces are not only a problem in prematurely born infants. In Gouyon's study, 24% of term infants ventilated for severe respiratory disorders developed pneumothoraces (6). Therefore, it is important to investigate ventilatory strategies which might reduce their incidence. In a randomised study comparing pressure-limited to volume-targeted ventilation, the hypothesis that volume-targeted ventilation would be associated with a reduction in the incidence of pneumothorax will be investigated.

1.1.5.3 Neurological complications

Ventilation strategy can influence neurological outcomes in the sick neonate primarily by the relationship of cerebral blood flow to the partial pressure of arterial

carbon dioxide ($PaCO_2$). Hypocarbia causes cerebral vasoconstriction and hypercarbia causes cerebral vasodilation. Wide and sudden fluctuations in $PaCO_2$ are thus undesirable. Hypocarbia is associated with increased risk of periventricular leukomalacia (PVL) and severe intraventricular haemorrhage (IVH) in prematurely born infants (35-37). In term infants with hypoxic ischaemic encephalopathy, hypocarbia was found to be associated with an increased risk of death or disability at 18 to 22 months (38). Prolonged hypocarbia is also associated with hearing loss in term and near-term infants (39). In a randomised study, the hypothesis that volume-targeted ventilation compared to pressure limited ventilation will reduce the incidence of hypocarbia will be tested.

1.2 Ventilator-induced lung injury / Ventilator-associated lung injury

As early as 1745 there was a report suggesting that mechanical inflation of human lungs may be injurious (40). This concept has now been extensively investigated and damage caused by artificial ventilation may be broadly grouped into four categories: barotrauma, volutrauma, atelectrauma and biotrauma (41). Lesions produced by mechanical ventilation in laboratory animal experiments have been termed ‘ventilator-induced lung injury’ (VILI) and the counterpart seen in humans in clinical practice is called ‘ventilator-associated lung injury’ (VALI).

1.2.1 Barotrauma

Gross anatomical damage caused to the lung by high positive pressures has been historically described as barotrauma. It is classically manifest as extra-alveolar air leaks such as pulmonary interstitial emphysema, pneumothorax and pneumomediastinum. Macklin’s study (42) demonstrated how an increased pressure gradient between the alveoli and vascular sheath led to entrance of air

into the interstitium. At the same time that Northway (15) described BPD in premature infants with RDS, Barnes and colleagues (43) published a report describing the radiological appearances, airways resistance, static and dynamic lung compliances, and histological characteristics of the lungs of six infants receiving prolonged positive pressure ventilation with high airway pressures. Those infants had been ventilated for respiratory insufficiency secondary to RDS, cardiac disease or pneumonia and ranged from one day to 13 weeks in age. High pressures had been used during ventilation, with mean peak inflation pressures starting off around 20-30 cm H_2O, but rising to 35-45 cm H_2O and at times up to 60-70 cm H_2O. The authors noted that the characteristics of the lungs in the group of infants closely resembled the chronic phase of BPD as described by Northway, yet only two of the six infants described had RDS or were ventilated with high oxygen concentrations. It was concluded that the lung damage might be attributed to the high pressures used during ventilation.

1.2.2 Volutrauma

In 1992, Dreyfuss and Saumon declared, “Barotrauma is volutrauma” (44). They put forward the case that it was actually high tidal volumes generated during positive pressure ventilation that caused lung damage. Animal studies have shown that increases in airway pressure without a corresponding increase in lung volume (achieved by restricting chest and abdominal wall movement by binding) did not produce the lung injuries seen in high peak pressure ventilation with no restriction of volume change (45-47). Injuries attributed to lung overinflation include increases in alveolar-capillary permeability, pulmonary oedema and ultrastructural damage such as discontinuities in alveolar type I cells (48), endothelial cell detachment exposing the basement membrane and endothelial

cell breakage (49). In lungs acutely injured prior to ventilation, overinflation was shown to cause more severely increased permeability and oedema than in normal lungs (50, 51). This suggests that infants ventilated for severe respiratory disorders may be more susceptible to volutrauma. The ARDS Network trial was stopped early when the interim analysis revealed a 22% reduction in mortality when adult ARDS patients were ventilated with 6ml/kg compared to 12ml/kg (52). This thesis will examine the impact of different levels of tidal volume targeting on the physiological outcome of work of breathing in infants born at term.

1.2.3 Atelectrauma

Suboptimal inflation of the lungs can also be damaging, and the effect of repetitive opening and collapse of distal airways has been termed atelectrauma. Robertson et al suggested that the force required to open up atelectatic areas in lungs affected with RDS may cause shear stress leading to epithelial disruption (53). Other mechanisms have been suggested as contributing to lung injury during low volume ventilation: decreased partial pressure of oxygen in atelectatic alveoli can cause cell damage and atelectasis can inhibit surfactant production and cause uneven distribution of surfactant. Another hypothesis put forward is that of increased regional stress during re-expansion of atelectatic areas situated adjacent to areas of normal expansion. Positive end-expiratory pressure (PEEP) has been shown to be protective against atelectrauma. Determining optimal lung recruitment manoeuvres and tidal volume targets would help in prevention as well. The deleterious effect of using tidal volumes that are too low has been highlighted in studies of preterm ventilation (54, 55). In this thesis, the effect of different levels of volume targeting will be assessed to determine the optimal volume to be used in a subsequent randomised trial.

1.2.4 Biotrauma

The mechanical factors that lead to barotrauma, volutrauma and atelectrauma have been associated with inflammatory mediator-related injury which has been termed biotrauma.

Pugin showed that human alveolar macrophage preparations subjected to cyclic stretch stimuli mimicking high tidal volume ventilation released interleukin 8 (IL-8), a chemokine that attracts neutrophils (56). Similar findings were reported by Vlahakis in human alveolar epithelial cells (57). This may explain the mechanism of neutrophil infiltration in VILI. In a series of experiments on isolated, unperfused rat lungs (58), all traumatic ventilation strategies [moderate volume (15ml/Kg), zero PEEP; high volume (40ml/Kg), zero PEEP] were associated with increased inflammatory cytokine levels in bronchoalveolar lavage (BAL) fluid.

Belperio showed that knockout mice for the MIP-2 receptor showed less VILI than wild-type mice when subjected to high tidal volume ventilation, suggesting an important role for IL-8 (human equivalent) in the pathogenesis of VALI (59).

Ranieri showed reduction in BAL and plasma concentrations of cytokines associated with lung-protective ventilation strategies (60). In a study of 30 preterm neonates with RDS randomised to receive volume guarantee (VG) ventilation at either 3ml/kg or 5ml/kg, Lista et al showed that the lower level was associated with a significantly higher level of BAL IL-8 on Day 7 ($p<0.05$) as well as a shorter duration of ventilation ($p=0.05$) (55).

1.2.5 Asynchrony

Asynchrony between the patient and ventilator is a mismatch between the patient's spontaneous respiratory efforts and the ventilator-delivered mechanical inflation.

Asynchronous ventilation adversely affects oxygenation and gas exchange in neonates and can lead to the need for higher airway pressures to achieve adequate gas exchange (61). Asynchrony increases the risk of air leaks (62). Asynchrony is associated with an increased work of breathing (63) and an increased duration of ventilation due to ineffective weaning (64). This thesis will examine patterns of interaction between ventilated term born infants' respiratory efforts and mechanical inflations and determine if there is any association between asynchronous interactions and modes of ventilation or volume target levels.

1.2.6 Ventilator-induced diaphragmatic dysfunction (VIDD)

Ventilator-induced diaphragmatic dysfunction is characterised by a decrease in the force-generating capacity of the diaphragm in a time-dependent manner in ventilated subjects and is related to disuse atrophy (65). It is mainly a complication of controlled ventilation modes and has been shown to be attenuated with assisted ventilation modes (66, 67). It has been demonstrated in animal studies (68, 69). Evidence is emerging that it occurs in humans (70, 71). Postmortem analysis revealed diffuse diaphragmatic muscle fibre atrophy in human neonates who were mechanically ventilated for 12 days or more immediately before death; those changes were not present in diaphragms of infants ventilated for seven days or less (72). VIDD could explain the difficulties encountered in weaning and discontinuation of mechanical ventilation in some patients. Hence it is important to carry out studies where clinical outcomes may be related to physiological measures of respiratory muscle function, to determine if diaphragmatic dysfunction is clinically important in ventilated neonates. In this thesis, volume-targeted

ventilation will be compared to pressure-limited ventilation to determine which mode is associated with superior respiratory muscle strength.

To protect the infant from VALI, VIDD and BPD, optimising ventilation so that rapid weaning and extubation can be facilitated is important. In this thesis, outcomes will include time to achieve specified weaning criteria and physiological measures quantifying WOB and respiratory muscle strength, to compare the efficacy of volume-targeted and pressure-limited ventilation.

1.3 Modes of ventilation

1.3.1 Conventional modes

1.3.1.1 Continuous Mandatory Ventilation (CMV)

Until the early 1970s, newborns were ventilated with modified adult ventilators. The earliest form of mandatory ventilation, intermittent positive pressure ventilation (IPPV) was delivered by these devices using intermittent gas flow. Spontaneous infant breaths were thought undesirable as the baby would rebreathe ‘dead air’ (73, 74). Clinicians concentrated on abolishing infant respiratory efforts with pharmacological paralysis or hyperventilation. The next generation of ventilators incorporated design features which provided a continuous flow of fresh gas allowing spontaneous breathing during mechanical ventilation (75). The provision of mechanical breaths at a fixed rate while allowing simultaneous spontaneous infant breathing was termed intermittent mandatory ventilation (IMV) (76). Non-synchronised IMV with a view to providing full ventilator support to the infant is commonly termed continuous mandatory ventilation (CMV) (77).

During CMV, the ventilator delivers the set peak inspiratory (PIP), inspiratory time and rate regardless of infant respiratory effort. Those characteristics mean that CMV may be associated with asynchronous patient-ventilator interactions. Asynchrony is associated with adverse effects such as impaired gas exchange, increased risk of air leak (62) and increased risk of IVH (78, 79). Greenough described the different patterns of patient ventilator interaction in ventilated preterm infants on CMV: active expiration against ventilator inflation was the second most common interaction and was associated with pneumothorax and poor blood gases (31).

1.3.1.2 Patient-triggered ventilation

By the 1990s, ventilator technology was sufficiently advanced to enable patient-triggered modes to be used in neonates. Various methods have been used to sense the patient inspiratory effort which triggers the delivery of a ventilator breath. Currently, flow-sensing pneumotachographs are widely used to deliver patient-triggered modes. Synchronised Intermittent Mandatory Ventilation (SIMV) and Assist/Control Ventilation (ACV) have been used most commonly in neonates. In SIMV, ventilator inflations at the rate set by the clinician are synchronised to the onset of spontaneous infant breaths. The infant is able to breathe spontaneously between ventilator inflations, but breaths above the preset ventilator rate are not supported. In ACV, every spontaneous infant inspiratory effort that exceeds the trigger threshold is supported by a mechanical inflation.

Triggered ventilation should, in theory, reduce asynchronous patient-ventilator interactions. Animal studies have shown preservation of diaphragm function using triggered modes compared to CMV (66, 67). A systematic review of patient-

triggered modes in newborns (33) showed that ACV/SIMV was associated with a shorter duration of ventilation compared to CMV (weighted mean difference -34.8 hours, 95% CI -62.1, -7.4). ACV was associated with a trend to a shorter duration of weaning compared to SIMV (weighted mean difference -42.4 hours, 95% CI -94.4, 9.6). Triggered ventilation was not associated with a significant reduction in the incidence of BPD.

1.3.2 Newer ventilation modes

1.3.2.1 Volume-targeted ventilation (VTV)

Volume-controlled ventilators have been in use for adults since the 1960s. In 1971, Kirby described a design for a new volume ventilator specifically targeted for neonatal and paediatric use accompanied by case reports describing its successful use in four infants (80). Despite the theoretical advantages of volume-targeted ventilation, it did not become prevalent in neonatal clinical practice or feature as the subject of further clinical studies in neonates until more than two decades later. This was because ventilator technology in the 1970s and 1980s was limited by various factors, including inability to measure the very small tidal volumes that characterise neonatal ventilation, compliant ventilator circuits which exacerbated loss of volume, and suboptimal trigger response times. In addition, the use of uncuffed endotracheal (ET) tubes in neonates means there is a variable leak around the ET tube, which affects the volume of gas actually delivered to the lungs. A new generation of ventilators driven by microprocessor technology and fitted with modern flow sensors, enabling tidal volume measurement near the infant’s airway and provision of leak compensation,

introduced the prospect of volume-targeted ventilation (VTV) in even extremely low birth weight neonates.

VTV is designed to deliver a consistent tidal volume with every inflation despite changing lung mechanics. This is accomplished by the microprocessor-based technology of modern ventilators which allows delivery of the mode according to algorithms written into software. During volume-targeted ventilation a set tidal volume is delivered within the limits of the maximum allowed PIP set by the clinician. Expiratory tidal volume is most commonly monitored and targeted as it is less affected by leak around the ET tube compared to inspiratory tidal volume. Volume-targeting can be used in conjunction with CMV, SIMV, ACV or pressure support.

VTV can be considered an ‘umbrella’ term encompassing a range of modes (Table 1.2). An *in vitro* lung model study (81) testing four different ventilators (Dräger Babylog 8000-plus, SLE 5000, Stephanie and VIP Bird Gold) showed that with the same settings in volume-targeted mode, the Stephanie and VIP Bird delivered significantly lower MAP and PIP and the SLE 5000 and VIP Bird delivered significantly shorter inflation times. These differences in performance could be related to the different pressure waveform produced by each ventilator. This thesis will investigate VTV delivered by the SLE 5000 ventilator running software version 4.3: the volume-targeted mode is termed TTV_{plus}.

Volume-targeted mode	Ventilator(s)	Brief description
Volume-guarantee (VG)	Dräger VN500, Babylog 8000-plus	Clinician selects target VT and maximum PIP. The ventilator uses the expiratory VT of the previous breath to determine gradual adjustment of PIP to reach the target VT over the next few breaths.
Targeted Tidal Volume plus (TTV^{plus})	SLE 5000	Clinician sets target VT and maximum PIP. The ventilator makes use of a 'test breath' every few breaths to make gradual adjustments of PIP to achieve the target VT.
Volume-limited Ventilation	Stephanie	Clinician sets a maximum VT 'limit'. If expiratory VT reaches this limit, PIP of the subsequent breath is reduced.
Pressure-Regulated Volume Control (PRVC)	Servo 300A, Servo-i	Clinician selects target VT and maximum PIP. An initial breath with PIP 10 cm of H_2O above PEEP is used as a reference to calculate PIP required to deliver set VT according to lung compliance. Automatic adjustments of PIP occur in steps of 3 cmH_2O to maintain set VT.
Volume-Assured Pressure Support (VAPS)	VIP Bird Gold	Clinician selects the target Vt. Breaths start off as pressure-support. Delivered VT is measured when inspiratory flow decelerates to the set minimum – if it exceeds the set VT the breath is terminated by flow-cycling, if it is less then inspiratory flow continues till set VT is achieved.
Volume-Support Ventilation	Servo-i	Clinician selects target VT, minute volume and rate. Patient determines the inspiratory time. Automatic adjustment of PIP in consecutive breaths until target VT is reached.
Pressure Augmentation	Bear 1000	Clinician selects minimum VT, ventilator adjusts flow to deliver this; PIP remains fixed.

Table 1.2 Volume-targeted ventilation modes

VTV would appear to hold great benefits: by providing a uniform tidal volume it would offer protection from volutrauma and atelectrauma. Autoweaning of PIP that is incorporated in this mode would prevent hypocarbia. A recent survey highlighted that VTV was routinely used in 60% of neonatal units in Australasia and 40% of units in Sweden, Denmark, Finland and Norway (82). The most common reason given for using VTV was that it reduces BPD. Systematic review of the results of twelve randomised controlled trials (RCTs), however, demonstrated that whereas use of VTV was associated with a significant reduction in pneumothoraces, grade 3-4 intraventricular haemorrhage/periventricular leukomalacia and the combined outcome of death or BPD, the reduction in BPD defined as oxygen dependency at 36 weeks postmenstrual age was of borderline significance, and there was no significant effect on BPD defined as oxygen dependency at 28 days (34). The RCTs included only prematurely born infants. It is not known whether VTV is being used in term infants despite the lack of evidence to support its use in this group. As part of this thesis, a national survey of ventilation practice relating to term born infants will be carried out.

Klingenberg's survey (82) highlighted considerable variation in VTV practice in that the median (range) of upper limits of target tidal volume were 5 (4-8) ml/kg for the initial ventilation of prematurely born infants and 6 (4-10) ml/kg for infants with ventilator-dependent BPD. Yet, the level of volume targeting influences the infant's work of breathing. In both acute respiratory distress (83) and during weaning (84), it has been demonstrated that use of 6 ml/kg compared to 4 ml/kg was associated with a significantly lower transdiaphragmatic pressure time product (PTP_{di}), which is a measure of the

work of breathing (WOB). Polimeni's study in preterm infants (54) showed that SIMV with a volume-target of 6ml/kg rather than 4.5ml/kg was associated with significantly reduced duration of hypoxaemic episodes compared to SIMV with no volume-target. Lista compared the effect of volume-targeting at 3ml/kg vs 5ml/kg in preterm infants (55). The 5ml/kg group had a shorter duraton of ventilation, just reaching statistical significance. The study analysed the level of pro-inflammatory cytokines in tracheal aspirate and found a significantly higher level of IL-8, a cytokine associated in the pathogenesis of BPD, on day 7 of the group ventilated with 3ml/kg. Those results suggest a role for the higher tidal volume in attenuating an inflammatory response in the acute stage of respiratory disease. These studies from Patel, Polimeni and Lista (54, 55, 83, 84) underline the fact that determining the optimal tidal volume to target is necessary before determining a protocol for comparing VTV to PLV in a randomised study. This thesis aims to determine the optimal level of tidal volume targeting in infants born at term with regard to the outcome of WOB. In a subsequent study, volume-targeted ventilation will then be compared to pressure-limited ventilation with assessment of short-term clinical and physiological outcomes.

1.3.2.2 Proportional Assist Ventilation (PAV)

In PAV, the clinician can set levels of elastic and resistive unloading to be delivered by the ventilator. The patient's spontaneous respiratory effort determines the triggering, amplitude and termination of mechanical breaths, which the ventilator provides by servo-control (85). Thus, theoretically, there could be perfect synchronisation of patient and ventilator. For neonates, a backup mode must be provided in conjunction with PAV to support periods of

inadequate respiratory effort (86). The aim of PAV is to match the ventilator to the infant's respiratory efforts so that the work of breathing of the infant is reduced. Thus in theory, it is possible to produce an inflation pressure wave which is in phase with the inspiratory volume of the infant in situations where the main mechanical problem is one of low lung compliance e.g. the respiratory distress syndrome, a technique known as elastic unloading, elastance being the reciprocal of compliance. Inflation pressure can also be produced in phase with the infant's inspiratory flow when resistance is high (resistive unloading).The infant controls the onset and termination of inspiration. The operator is helped in this as the ventilator displays both the compliance and the resistance of the respiratory system.

Proportional assist ventilation (PAV) was first recommended as an alternative and potentially less damaging form of respiratory support for neonates in 1998 (87) but has been slow to be adopted and not yet subjected to large randomised clinical trials. In acute respiratory disease in prematurely born infants, PAV was associated with maintenance of gas exchange with lower transpulmonary pressure swings compared to CMV and ACV in a crossover study (88). In evolving chronic lung disease in prematurely born infants, PAV was shown to provide satisfactory gas exchange at lower mean airway pressures compared to SIMV and ACV in a crossover study (86). PAV has also been demonstrated to reduce thoraco-abdominal asynchrony and chest wall distortion in preterm infants (89).

One of the reasons PAV has not been assessed in larger studies is that optimal settings have yet to be identified. Schulze (87) showed that high levels of unloading lead to runaway inspiratory pressure oscillations,

particularly when the resistance is low. In addition, a recent *in vitro* study (90) using a dynamic lung model found that although progressive unloading led to largely matched increases in airway opening pressures and reductions in "pleural" pressures, there was a delay in the onset of inflation and occurrence of oscillations in the pressure waveform at certain levels of unloading depending on the characteristics of the lung model. It also remains unclear of the extent to which the runaway pressure oscillations might affect the infant's WOB. In this thesis, the effect of PAV on elastic and resistive WOB will be assessed *in vitro*.

1.4 Outcome measures

1.4.1. Physiological measurements

1.4.1.1 Work of breathing

The anatomy and physiology of newborns predisposes them to an increased work of breathing. Their predominantly cartilaginous ribcage is highly compliant; this effect is more pronounced with decreasing gestational maturity. They spend a large proportion of time in rapid eye movement sleep; the consequent inhibition of intercostal muscle tone further destabilises the thoracic cage. A significant amount of the force generated by diaphragmatic contraction is thus lost in distortion of the ribcage as opposed to production of inspiratory flow.

The resistance of a muscle to fatigue correlates with its proportion of high-oxidative muscle fibres. In prematurely born neonates, the diaphragm contains only 10% type I (slow-twitch, high-oxidative) fibres, in term infants the proportion of type I fibres is 25% and in children over 2 years of age it is 55% (91). Thus the

diaphragm of the newborn, particularly if premature, is more susceptible to fatigue. Total abolition of WOB in ventilated infants is undesirable. Inactive muscles rapidly lose oxidative capacity (92) and thus become more prone to fatigue. In an adult human study, marked atrophy of diaphragm myofibrils was demonstrated with as little as 18 hours of diaphragmatic inactivity (70). Excessive WOB in ventilated neonates has adverse consequences. Increased metabolic requirements from high WOB increase susceptibility to fatigue (93): this has the effect of the infant requiring more support from the ventilator, thus prolonging weaning (94). The caloric requirements of increased WOB may adversely impact on infant growth at a critical stage in their development. Infants with a high WOB are more likely to fail extubation (95). Previous studies (83, 84) have shown that in preterm infants, volume-targeting at 6ml/kg compared to 4ml/kg was associated with a significantly lower WOB. This thesis aims to determine the optimal level of volume targeting in term infants with regard to the outcome of WOB. Once the optimal volume-targeting level has been determined, this thesis will test the hypothesis that VTV will be associated with a significantly lower WOB compared to PLV.

1.4.1.2 Respiratory muscle strength

The strength of the respiratory musculature is represented by its contractile force, which is directly proportional to spontaneously generated airway pressures. In neonates, assessment of respiratory muscle strength can be made by recording the maximal negative and positive pressures generated during crying against airway occlusion at functional residual volume and total lung capacity respectively (96). These measurements are termed Pimax and Pemax, as they represent the maximal inspiratory and expiratory pressures

respectively the subject is able to generate. This thesis aims to investigate whether respiratory muscle strength is superior with volume-targeted ventilation compared to pressure-limited ventilation.

1.4.2. Duration of ventilation

While mechanical ventilation is essential in management of neonatal respiratory failure, it is desirable to wean the infant from the ventilator as soon as possible so as to avoid risks associated with VILI/VALI. For the RCT comparing volume-targeted to pressure-limited ventilation in prematurely born infants, the time to achieve pre-specified weaning criteria has been chosen as the main outcome measure.

1.4.3 Hypocarbia

Hypocarbia is an abnormally low partial pressure of carbon dioxide within arterial blood. Mechanically ventilated infants are at risk of developing hypocarbia. Carbon dioxide regulates cerebral blood flow in neonates (97), and both preterm and term neonates show a reduction in cerebral perfusion in response to hypocarbia (98). Erickson's study (35) reported significantly increased risk of severe IVH or PVL if hypocarbic (pCO_2 < 4 kPa) in the first 48 hours of life and of BPD if hypocarbic on at least three occasions in the first 24 hours of life. In the 2010 Cochrane review of volume-targeted versus pressure-limited ventilation in prematurely born neonates (34), hypocarbia was a secondary outcome measure analysed and was defined as pCO_2 less than 4.7 kPa. In the randomised study comparing volume-targeted to pressure-limited ventilation in preterm neonates carried out as part of this thesis, hypocarbia in the first 72 hours of life is reported as a secondary

outcome and is defined as a value of pCO_2 of less than 4.5 kPa on any blood gas.

1.5 Patient-ventilator interactions

In most circumstances, some degree of respiratory effort is retained by a mechanically ventilated infant. In ventilated neonates, interactions with the ventilator may be produced by the elicitation of respiratory reflexes by the delivery of a mechanical breath. These interactions were described in detail by Greenough et al in ventilated prematurely born infants (31) and can be classified into four distinct patterns as follows:

- Inspiration coinciding with ventilator inflation (synchrony)
- Active expiration against ventilator inflation
- Prolongation of spontaneous expiration during ventilator inflation
- Deep inspiration coinciding with ventilator inflation (augmented inspiration)

1.5.1 Synchrony

In this pattern the infant's spontaneous breath coincides with the mechanical breath. No respiratory reflexes are involved.

1.5.2 Active expiration

Here, the infant actively expires against the ventilator breath. This may be brought about by the stimulation of the Hering-Breuer expiratory reflex in the infant by the mechanical positive pressure breath stimulating pulmonary slowly adapting stretch receptors. The Hering-Breuer expiratory reflex was described in 1868 – prolonged inflation of the lungs of anaesthetised animals elicited an active expiratory effort (99).

1.5.3 Prolongation of expiration

In this pattern, passive expiration continues for longer than expected because of a decrease in spontaneous inspirations. This pattern of patient-ventilator interaction is thought to be produced by elicitation of the Hering-Breuer inflation reflex in the infant by the mechanical breath. In the Hering-Breuer inflation reflex, distension of the lungs in mechanically ventilated animals led to a decrease in the frequency of inspiration (99). This reflex has been shown to occur in human neonates (100).

1.5.4 Augmented inspiration

These exaggerated inspirations coinciding with a mechanical breath are thought to be due to provocation of Head's paradoxical reflex. This reflex was first described by Head (101) as a prolonged, forceful contraction of the diaphragm during rapid lung inflation on a background of vagal blockade. In neonates it is likely produced by stimulation of vagally-innervated irritant receptors within the large airways.

It is not known whether term infants display similar interactions influenced by respiratory reflexes. Delineating how term born infants interact with mechanically delivered breaths may help in optimisation of ventilation in this group. This thesis will attempt to identify and analyse patterns of patient-ventilator interaction in term born infants.

1.6 Hypothesis

The majority of studies assessing neonatal ventilation have been carried out on prematurely born infants. This thesis will focus on optimisation of ventilation in term born infants. The hypotheses to be tested are:

- There will be significant differences in ventilation practice relating to infants born at term
- Higher levels of volume-targeting will be associated with lower work of breathing in infants born at or near term
- In prematurely born infants with acute respiratory failure, volume-targeted ventilation will be superior to pressure-limited ventilation
- Infants born at term will display interactions with ventilator inflations similar to prematurely born infants
- Elastic and resistive unloading with PAV will be equally effective in reducing the work of breathing of a lung model.

1.7 Aims

- To carry out a national survey of ventilation practice in infants born at term.
- In infants born at or near term, determination of the optimal tidal volume target which will be associated with the lowest work of breathing as reflected by PTP_{di}.
- Randomised comparison of volume-targeted and pressure-limited ventilation in prematurely born infants, assessing outcomes of time to achieve weaning criteria, work of breathing and respiratory muscle strength.
- Analysis of patient-ventilator interactions in term born infants to determine if there is any difference in interactions on mandatory versus triggered ventilation or related to differences in volume-targeting.
- Optimisation of PAV methodology using a dynamic lung model.

Chapter 2: Methods

2.1 Studies

- National survey examining clinical practice in relation to respiratory support in term infants
- Comparison of different levels of tidal volume targeting in term infants
- Randomised comparison of volume-targeted and pressure-limited ventilation in preterm infants
- Description of spontaneous respiratory activity in ventilated term infants and comparison of patient-ventilator interactions
- *In vitro* study analysing effects of proportional assist ventilation (PAV) on the work of breathing

2.2 Ethics

The clinical studies were approved by the King's College Hospital Research Ethics committee. Infants were recruited from the neonatal intensive care unit at King's College Hospital, London. Written, informed consent was obtained from the infant's parent(s).

2.3 Clinical studies

2.3.1 Equipment

2.3.1.1 Measurement of flow and airway pressure

A pneumotachograph (Mercury F10L, GM Instruments, Kilwinning, Scotland) was used to measure flow of gas. It was inserted between the endotracheal tube and ventilator Y-piece (Figure 2.1) and connected to a differential pressure transducer (MP45, range ± 2 cm H_2O, Validyne, Northridge, CA, USA). Airway pressure was measured via tubing from the side port of the pneumotachograph connected to another differential pressure transducer (MP45, range ± 100 cm H_2O Validyne Corp, Northridge CA, USA). The signals from the pressure transducers were amplified using a carrier amplifier (CD 280, Validyne, Northridge, CA, USA).

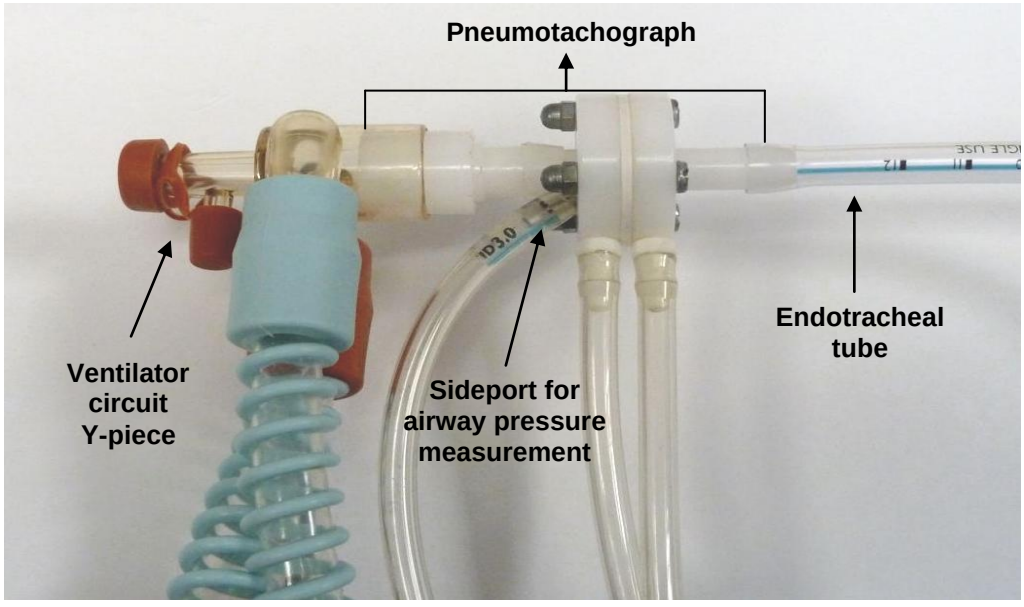


Figure 2.1 Pneumotachograph inserted between endotracheal tube and ventilator circuit Y-piece

2.3.1.2 Measurement of oesophageal and gastric pressures

Measurement of oesophageal (P_{oes}) and gastric pressures (P_{gas}) was carried out using a flexible, silicone-coated catheter (7 French gauge) and fitted with two microtransducers five centimetres apart (Model CTO-2; Gaeltec Ltd, Dunvegan, Scotland, UK) (Figure 2.2). Each sensor consisted of a metal diaphragm with directly deposited resistive strain gauges. The silicone coating on the sensing area allowed a small amount of water absorption which could cause a baseline drift hence the catheter was soaked for a total of two hours prior to use to allow stabilisation of the baseline. The distal transducer (gastric) was located three mm from the catheter tip. The length of insertion of the catheter was estimated using the method for insertion of an orogastric or nasogastric tube (102). The catheter tip was lubricated with a small amount of sterile aqueous gel (Aquagel, Williams Medical Supplies, Gwent, Wales, UK). The aim was to position the distal transducer in the stomach and the proximal transducer in the lower third of the oesophagus. Correct placement of the catheter was confirmed by checking that there was good agreement between oesophageal and airway pressure changes during an airway occlusion, with the P_{oes}/P_{ao} ratio between 0.9 and 1.10 (103). Signals from the catheter were amplified via a dedicated transducer control unit (Model S7b Gaeltec Ltd, Dunvegan, Scotland, UK).

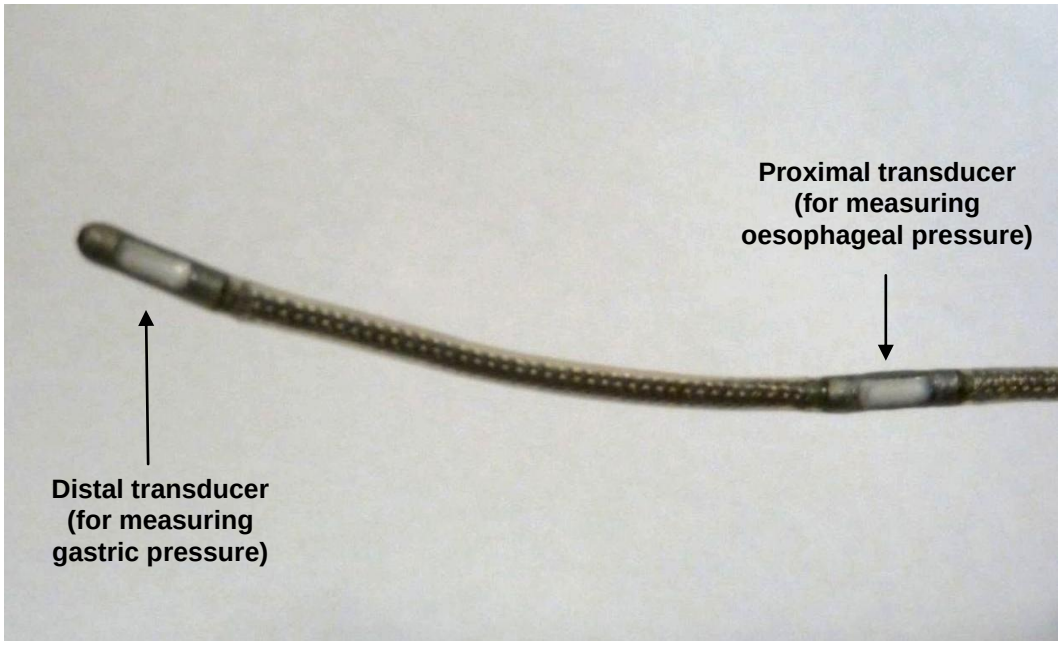


Figure 2.2 Tip of catheter used for oesophageal and gastric pressure measurements

2.3.1.3 Calibration

Calibration of airway pressure, flow, and dual microtransducers were carried out prior to each measurement. A two point calibration of pressure transducers was performed using a portable pressure meter (Comark, Welwyn Garden city, UK). The linearity of the Comark pressure meter was tested against a water manometer (Figure 2.3). Flow was calibrated using a low flow rotameter (0-12 L/min Platon, Roxspur Measurement & Control Ltd, Bramley, Hants, UK).

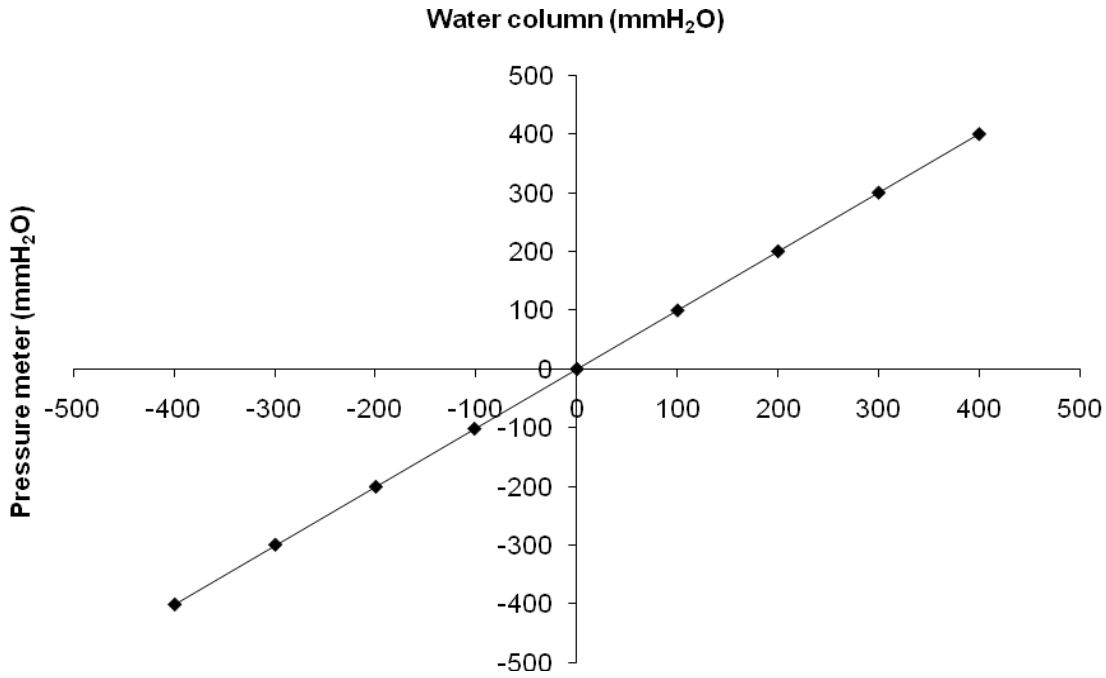


Figure 2.3 Linearity of Comark pressure meter tested against a water column

2.3.2 Linearity of systems

Linearity of each system used to measure oesophageal, gastric and airway pressure was tested by plotting pressure input to the individual transducer via the Comark pressure meter against the digitised output displayed by the software programme. Linearity was demonstrated for oesophageal and gastric pressure measurement between -50 to 50 cm H_2O pressure and for airway pressure measurement between -150 cm H_2O and 150 cm H_2O (Figures 2.4-2.6).

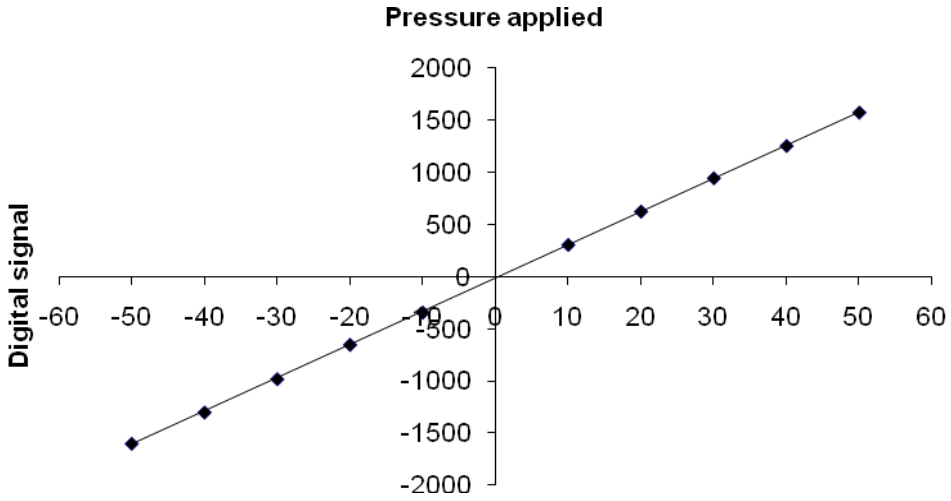


Figure 2.4 Linearity of oesophageal pressure transducer

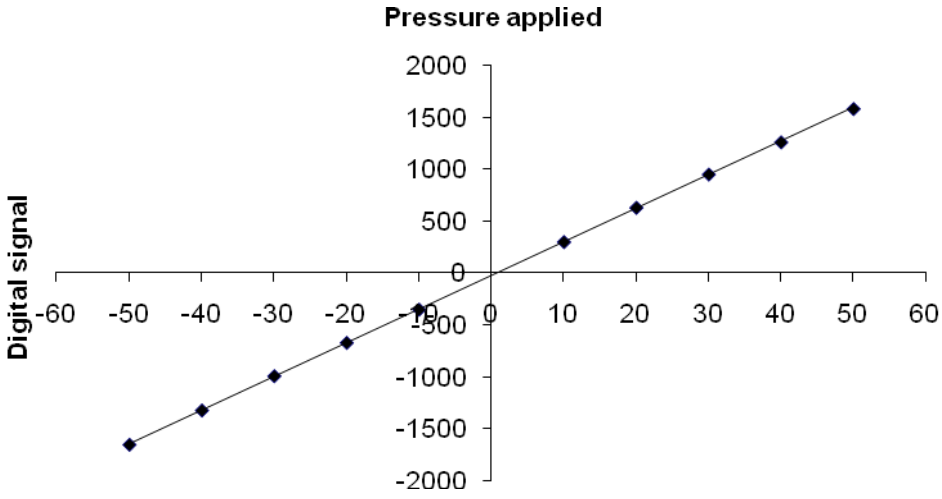


Figure 2.5 Linearity of gastric pressure transducer

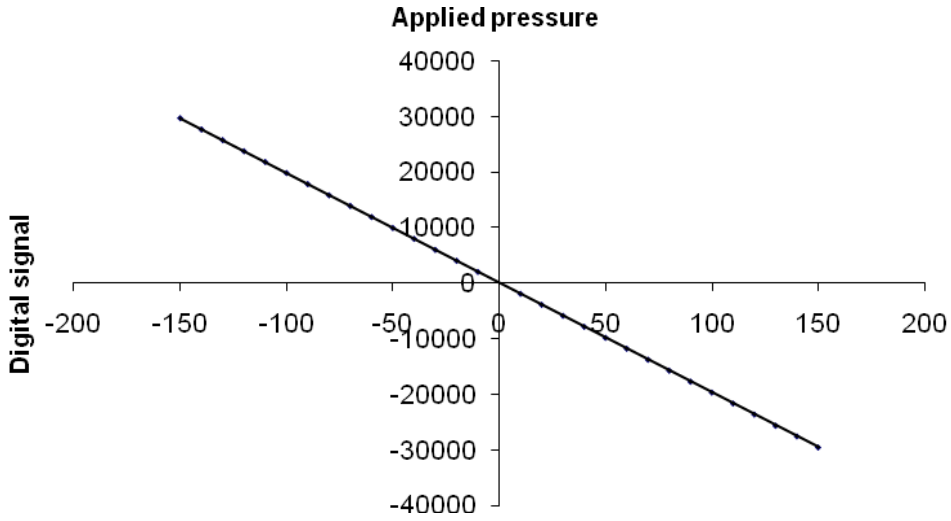


Figure 2.6 Linearity of airway pressure transducer

Linearity of the system used to measure flow of gas was tested by plotting flow input via the rotameter to the pressure transducer against the digitised output displayed by the software programme. The system was tested for four different percentages of oxygen: 21%, 30%, 50% and 100% (Figure 2.7).

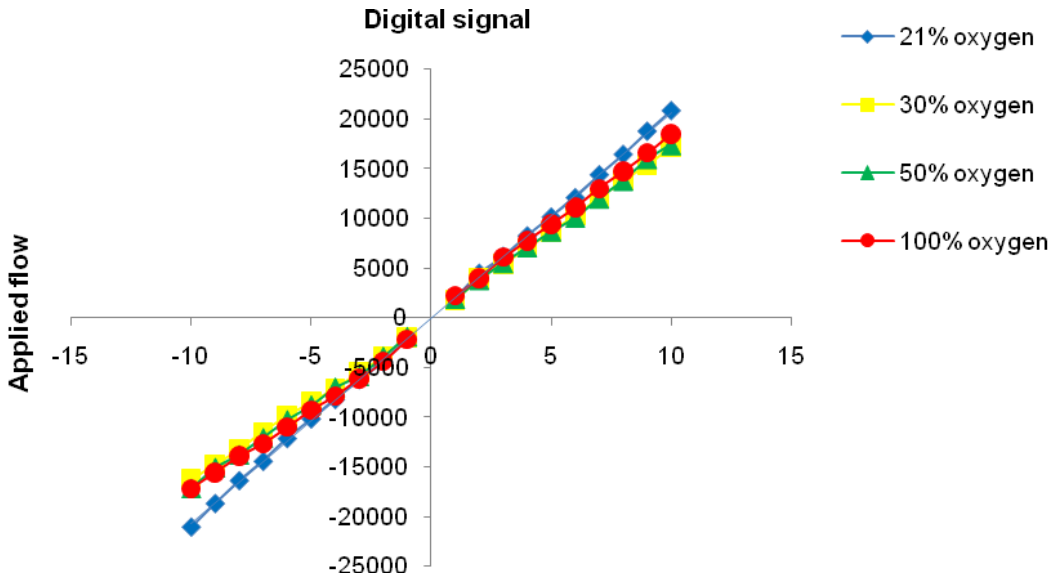


Figure 2.7 Linearity of flow measurement

2.3.3 Frequency response

The signal frequency range of an airway, oesophageal or gastric pressure wave response is determined by the respiratory rate, which for a neonate may fall between the range of 60 to 120 breaths per minute. Therefore the fundamental frequency (the first harmonic) is 1-2 Hz. The first ten harmonics contribute to the pressure waveform. Ideally the frequency response of the measuring system should be at least ten times the frequency of the infant's respiratory efforts, i.e. 20 Hz, to enable it to reproduce the first ten harmonics of the pressure wave without distortion.

Frequency response can be determined by a 'pop test' (104) in which an inflated balloon is fitted over the signal input site and then burst, producing an instantaneous negative step input to the system. The frequency response of the system (f3db) is calculated using the equation f3db =1/3 x $T_{r,}$ where T_r (response time) is defined as the time taken for pressure to fall from 90% to 10% of the initial pressure.

The frequency response of each system used was determined using the pop test method, with the change in pressure against time recorded on a computer (MacBook, Apple Computer Corp, Cupertino, California, USA) using Chart software (Version 5.0, ADInstruments Pty Ltd, Bella Vista, NSW Australia) with analogue-to-digital sampling at 40KHz (Powerlab, ADInstruments Pty Ltd, Bella Vista, NSW, Australia).

The frequency response of the airway pressure transducing system (consisting of the pressure transducer, connecting tubing, amplifier and computer) was determined by placing the tubing which connected the transducer to the pneumotachograph sideport inside an inflated balloon,

which was then burst. The response time was 0.8 milliseconds, giving a calculated frequency response of 416 Hz.

The frequency response of the flow measurement system (consisting of the pneumotachograph, connecting tubing, pressure transducer for flow, amplifier and computer) was determined by placing one end of the pneumotachograph within an inflated balloon. By partially occluding the other end of the pneumotachograph, a constant background flow was produced, during which the balloon was burst. The response time was 9 milliseconds, giving a calculated frequency response of 37 Hz.

The frequency response of the oesophageal and gastric pressure transducing system (consisting of the dual microtransducer-tipped catheter, amplifier and computer) was tested by placing the catheter inside an inflated balloon which was then burst. The response time was 3.6 milliseconds for the oesophageal pressure transducer and 3 milliseconds for the gastric pressure transducer, giving frequency responses of 92.5 Hz and 111 Hz respectively.

2.3.4 Data acquisition and storage

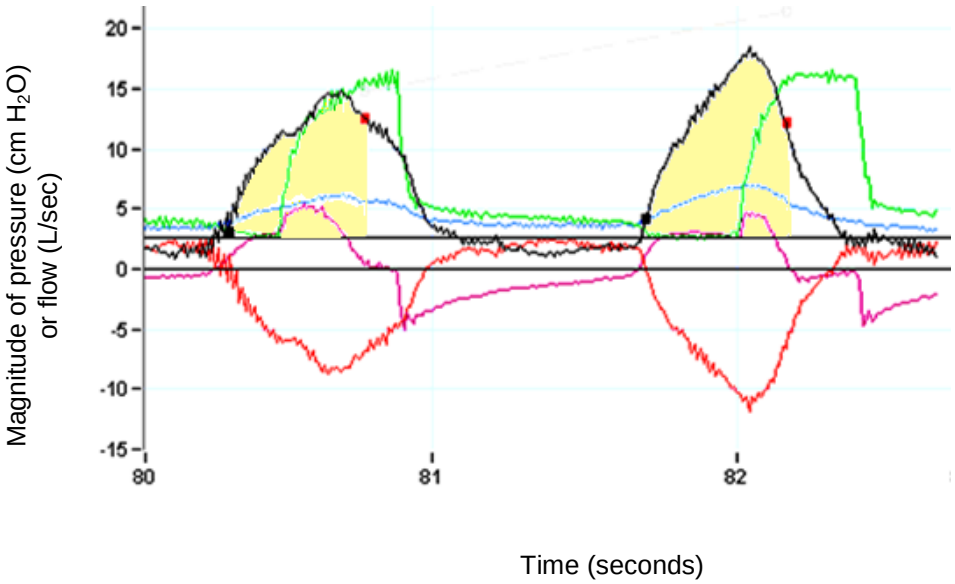
Amplified signals from the dual pressure catheter, flow and airway pressure transducers were displayed in real time on a laptop (Latitude CP*i* Dell Inc, Round Rock, Texas, USA) with a customised software application (Labview Ver 5.0, National Instruments, Austin TX, USA) with 100 Hz analogue-to-digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin, Texas, USA). Tidal volume data was generated within the software programme by digital integration of the flow signal. The data displayed in real time were recorded as per study protocol relating to physiological

measurements and stored as systematically-labelled files on the hard drive of the laptop for analysis.

2.3.5 Physiological measurements

2.3.5.1 PTP_{di}

Transdiaphragmatic pressure was calculated by the digital subtraction of the oesophageal from the gastric pressure. PTP_{di} was calculated by integration of the transdiaphragmatic pressure signal with time for each breath and expressed per minute. PTP_{di} recordings were carried out for a period of five minutes during quiet breathing. For analysis, a section of the recording providing 20 consecutive artefact-free breaths was selected. The Labview software calculated the PTP_{di} by digital integration of transdiaphragmatic pressure over inspiratory time ($PTP_{di} = \int P_{di}.T_i$); the mean of 20 consecutive infant respiratory efforts was taken.



- **Green** line represents airway pressure
- **Red** line represents oesophageal pressure
- **Blue** line represents gastric pressure
- **Black** line represents transdiaphragmatic pressure
- **Purple** line represents flow

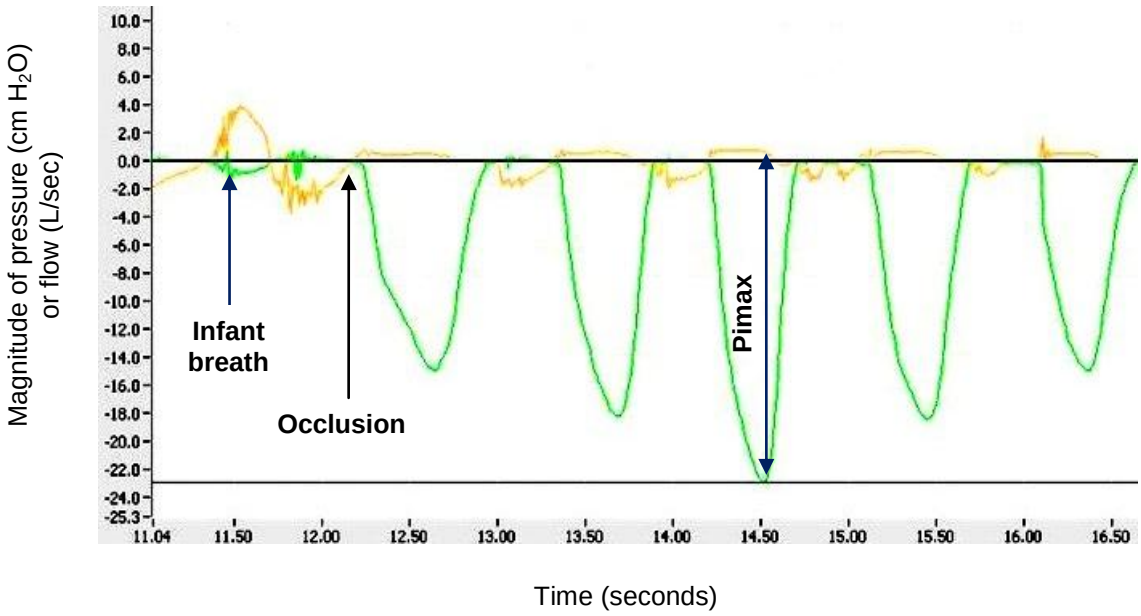
- Beginning of inspiration as denoted by flow crossing zero in the positive direction
- End of inspiration as denoted by flow crossing zero in the negative direction

The yellow shaded portion under the transdiaphragmatic pressure curve represents the PTP_{di}.

Figure 2.8 PTP_{di} trace

2.3.5.2 Pimax

Pimax is the measure of maximal inspiratory pressure during crying. In ventilated, prematurely born infants, this was measured by disconnecting the baby from the ventilator and fitting a T-shaped two-way valve to the end of the pneumotachograph connected to the infant's ETT tube. The inspiratory limb of the valve was occluded at end-expiration for five consecutive respiratory efforts before reconnecting to the ventilator. Three such recordings of five breaths were performed with an interval of a minute between each recording. The largest negative airway pressure generated during occlusion was recorded as the Pimax. If the infant desaturated or had bradycardia during the occlusion, they were immediately reconnected to the ventilator and given supplementary oxygen if necessary.



Green line represents airway pressure

Orange line represents flow

Figure 2.9 Pimax trace

2.4 In vitro study

2.4.1 Equipment

2.4.1.1 Dynamic lung model

The lung model was developed to represent the respiratory distress syndrome (RDS). Its unique aspect was that it incorporated a rigid external covering and a synthetic diaphragm, thus modelling a ‘pleural space’. This dynamic lung model consisted of a commercial lung model (SLE silicon test lung, part no. N6647; SLE, South Croydon, UK) mounted inside a rigid plastic cylinder (Figure 2.10). The commercial lung model outlet was externalised through the base of the cylinder and attached to the ventilator circuit via a pneumotachograph. The open end of the cylinder was covered by a latex rubber film, which represented the ‘diaphragm’. Repeated movement of the rubber film backwards and forwards simulated ‘diaphragmatic’ movements. The pressure changes within the cylinder, described as ‘pleural pressure’ (P_{pl}), were monitored from an outlet on the side of the cylinder using a second pressure transducer.

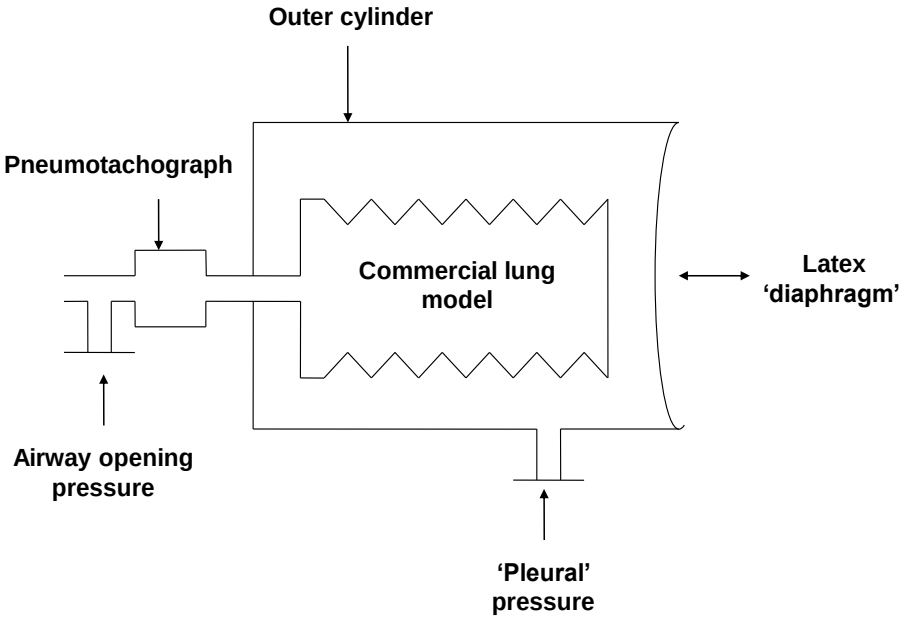


Figure 2.10 Diagram of dynamic lung model representing RDS

The compliance and resistance of the lung model were assessed using the Stephanie ventilator in pressure limited mode. The compliance of the lung model was 0.4ml/H_2O and the resistance 200 cmH_2O/L/sec. The resistance was generated by incorporating a length of narrow plastic tubing between the lung model and the pneumotachograph.

2.4.1.2 Measurements

Airflow was measured by a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (MP45, range±2 cm H2O; Validyne, Northridge, California, USA). Tidal volume was obtained by digital integration of the flow signal. The

pneumotachograph was inserted between the ‘neck’ of the lung model and ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45, range±100 cm H2O; Validyne). The signals from the pressure transducers were amplified using a carrier amplifier (CD 280; Validyne). P_{pl} was recorded using a differential pressure transducer (MP45, range±100 cm H2O; Validyne). The pressure and flow signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) using Spectra® software v 3.0.0.9 (Grove Medical, Hampton, UK) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50; National Instruments, Austin, Texas, USA). Calibration of equipment was carried out was performed as described in section 2.3.1.3 of this chapter.

Chapter 3: National survey of ventilation practice in term born infants

3.1 Introduction

There is limited evidence on the efficacy of respiratory support in infants born at term. The aim of this study was to test the hypothesis that there would be wide variation in the use of ventilation techniques in this patient group. A survey of ventilation practice in neonates born at term in the United Kingdom was performed.

3.2 Methods

An electronic web-based survey on respiratory support in neonates born at term was designed (Appendix A1). Lead clinicians of all neonatal units in the United Kingdom were identified using the BLISS directory, and contact details confirmed by contacting each hospital. Clinicians were sent an email inviting them to complete the online survey via a link. Non-respondents were followed up with further emails and a paper copy by post if they had not responded to emails.

3.2.1 Statistical analysis

Differences between levels of neonatal care were assessed for statistical significance using the Chi-squared test. Analysis was carried out using Graphpad Prism 5.0 (GraphPad, La Jolla, CA).

3.3 Results

The response rate was 82%, with 174 units of the 212 neonatal units in the UK providing responses. 90% of all neonatal intensive care units (NICUs), 96% of all local neonatal units (LNUs) and 56% of all special care units (SCUs) in the UK replied.

3.3.1 Number of term newborns ventilated according to unit level

Most NICUs (49%) and LNUs (58%) ventilated between 10 and 50 term newborns on an annual basis, with a large proportion of NICUs (42%) ventilating more than 50. The majority of SCUs (68%) ventilated less than 10 term newborns annually. (Figure 3.1)

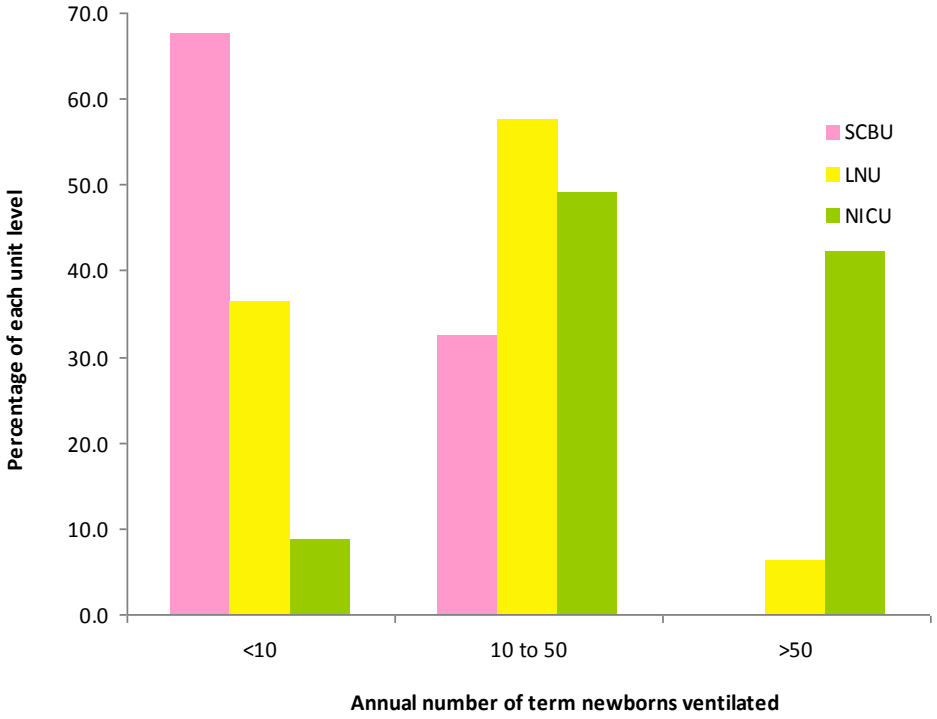


Figure 3.1 Percentage of units according to number of ventilated term newborns

3.3.2 Ventilators used

The three most frequently used ventilators for conventional ventilation were the SLE 5000, Dräger Babylog 8000/8000plus and SLE 2000. The SLE 5000 was used by 51% of responding NICUs and LNUs and 11% of SCBUs. The Dräger Babylog 8000/8000plus was used by 35% of NICUs, 23% of LNUs and 19% of SCBUs. The SLE 2000 was used by 19% of NICUs, 26% of LNUs and 57% of SCBUs. Many units use more than one type of ventilator.

High frequency oscillatory ventilation (HFOV) was provided by all NICUs. Amongst NICUs, the SLE 5000 was used by 49% to provide HFOV, the Sensormedics 3100A was used by 47% and the Stephanie was used by 18%. Of the responding LNUs, 48% (38 of 80 LNUs) specified they did not provide HFOV. Of the LNUs that did provide HFOV, 91% used the SLE 5000, 14% used the Dräger Babylog 8000plus/VN500 and 7% used the Sensormedics 3100A.

3.3.3 Primary mode of ventilation according to diagnosis

Units were asked to indicate which mode they would initiate ventilation for meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), congenital pneumonia/aspiration, non-respiratory causes of respiratory failure such as hypoxic ischaemic encephalopathy (HIE), congenital diaphragmatic hernia (CDH) and gastrointestinal (GI) surgery. The responses for CDH and GI surgery were not analysed for LNUs or SCUs as the majority did not respond to this question.

NICUs used volume-targeting significantly more than LNUs and SCUs during mechanical ventilation across the range of pathologies, particularly in RDS ($p=0.0006$) and congenital pneumonia ($p=0.0005$). In MAS and PPHN, HFOV was used as a primary ventilation strategy significantly more by NICUs compared to LNUs and SCUs (Table 3.1).

		NICU (n=57)	LNU (n=80)	SCU (n=37)	p value
MAS	**CPAP**	2 (4%)	19 (24%)	10 (27%)	0.002
	CMV	15 (26%)	36 (45%)	16 (43%)	0.069
	SIMV	21 (37%)	19 (24%)	8 (22%)	0.158
	ACV	14 (25%)	5 (6%)	3 (8%)	0.004
	PS	0	0	0	NA
	Volume-targeted	8 (14%)	6 (8%)	0	0.049
	HFOV	3 (5%)	0	0	0.044
RDS	**CPAP**	19 (33%)	38 (48%)	20 (54%)	0.103
	CMV	8 (14%)	17 (21%)	9 (24%)	0.409
	SIMV	17 (30%)	23 (29%)	5 (14%)	0.153
	ACV	11 (19%)	2 (3%)	3 (8%)	0.003
	PS	0	0	0	NA
	Volume-targeted	15 (26%)	8 (10%)	0	0.0006
	HFOV	0	0	0	NA
PPHN	**CPAP**	0	8 (10%)	4 (11%)	0.043
	CMV	17 (30%)	42 (53%)	24 (65%)	0.002
	SIMV	17 (30%)	18 (23%)	7 (19%)	0.433
	ACV	11 (19%)	6 (8%)	2 (5%)	0.044
	PS	0	0	0	NA
	Volume-targeted	8 (14%)	4 (5%)	0	0.021
	HFOV	11 (19%)	4 (5%)	0	0.001
Congenital pneumonia/ aspiration	**CPAP**	8 (14%)	24 (30%)	16 (43%)	0.007
	CMV	10 (18%)	28 (35%)	13 (35%)	0.059
	SIMV	23 (40%)	23 (29%)	6 (16%)	0.042
	ACV	13 (23%)	3 (4%)	2 (5%)	0.0008
	PS	0	0	0	NA
	Volume-targeted	12 (21%)	4 (5%)	0	0.0005
	HFOV	0	0	0	NA
Non-respiratory causes, eg. HIE	**CPAP**	3 (5%)	18 (23%)	6 (16%)	0.023
	CMV	13 (23%)	33 (41%)	20 (54%)	0.007
	SIMV	26 (46%)	23 (29%)	9 (24%)	0.05
	ACV	10 (18%)	5 (6%)	2 (5%)	0.054
	PS	2 (3.5%)	0	0	NA
	Volume-targeted	10 (18%)	4 (5%)	0	0.004
	HFOV	0	0	0	NA

Table 3.1 Initial mode of ventilation by diagnosis and level of neonatal care

3.3.4 Rescue mode of ventilation in term newborns

Units were asked which mode they would use as rescue if a term newborn deteriorated on the primary mode. In the event of an infant deteriorating on the primary mode, CMV was utilised significantly more by LNUs and SCUs compared to NICUs ($p<0.0001$) while HFOV was utilised, significantly more by NICUs compared to LNUs and SCUs ($p<0.0001$) (Table 3.2). Thirty percent of LNUs and 49% of SCUs stated in the comment box that a deteriorating infant would be transferred to a higher level of unit.

Units were asked if they routinely changed an infant on HFOV to conventional ventilation prior to extubation. Only data for NICUs were analysed for this question as HFOV is a mode of ventilation used mostly by NICUs; 61% of NICUs changed infants from HFOV to conventional ventilation prior to extubation and 39% extubated directly from HFOV.

		NICU (n=57)	LNU (n=80)	SCU (n=37)	p value
MAS	**CMV**	3 (5%)	31 (39%)	20 (54%)	<0.0001
	SIMV	1 (2%)	9 (11%)	8 (22%)	0.008
	ACV	1 (2%)	11 (14%)	2 (5%)	0.032
	HFOV	50 (88%)	27 (34%)	4 (11%)	<0.0001
RDS	**CMV**	3 (5%)	36 (45%)	21 (57%)	<0.0001
	SIMV	6 (11%)	9 (11%)	9 (24%)	0.111
	ACV	4 (7%)	10 (13%)	3 (8%)	0.527
	HFOV	43 (75%)	22 (28%)	2 (5%)	<0.0001
PPHN	**CMV**	4 (7%)	27 (34%)	18 (49%)	<0.0001
	SIMV	0	10 (13%)	7 (19%)	0.006
	ACV	1 (2%)	7 (9%)	2 (5%)	0.221
	HFOV	51 (90%)	30 (38%)	4 (11%)	<0.0001
Congenital pneumonia / aspiration	**CMV**	5 (9%)	36 (45%)	19 (51%)	<0.0001
	SIMV	2 (4%)	9 (11%)	10 (27%)	0.003
	ACV	3 (5%)	10 (13%)	2 (5%)	0.243
	HFOV	44 (77%)	20 (25%)	3 (8%)	<0.0001
HIE	**CMV**	9 (16%)	42 (53%)	21 (57%)	<0.0001
	SIMV	1 (2%)	11 (14%)	9 (24%)	0.004
	ACV	5 (9%)	9 (11%)	2 (5%)	0.591
	HFOV	38 (67%)	12 (15%)	2 (5%)	<0.0001

Table 3.2 Rescue mode of ventilation by diagnosis and level of neonatal care

3.3.5 Volume-targeted ventilation (VTV) in term newborns

26% of NICUs and 11% of LNUs, but no SCUs. indicated that they used VTV routinely in term newborns.

3.3.5.1 Volume-target (VT) ranges during VTV

Responses indicated a wide variety of VT ranges were used, with 4-6ml/kg and 6-8ml/kg being most commonly used in NICUs and 4-6ml/kg and 4-5ml/kg being most commonly used in LNUs (Figures 3.2 and 3.3). For LNUs, the lowest VT specified was 3.5ml/kg while the highest was 10ml/kg. For NICUs, the lowest VT specified was 3ml/kg while the highest was 8ml/kg.

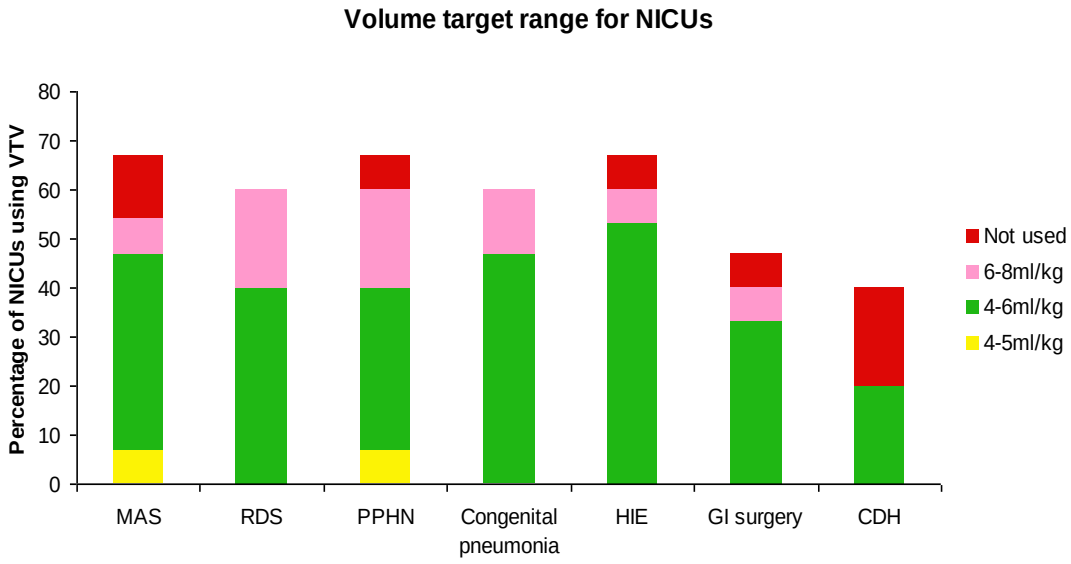


Figure 3.2 Commonly used target volume ranges in NICUs

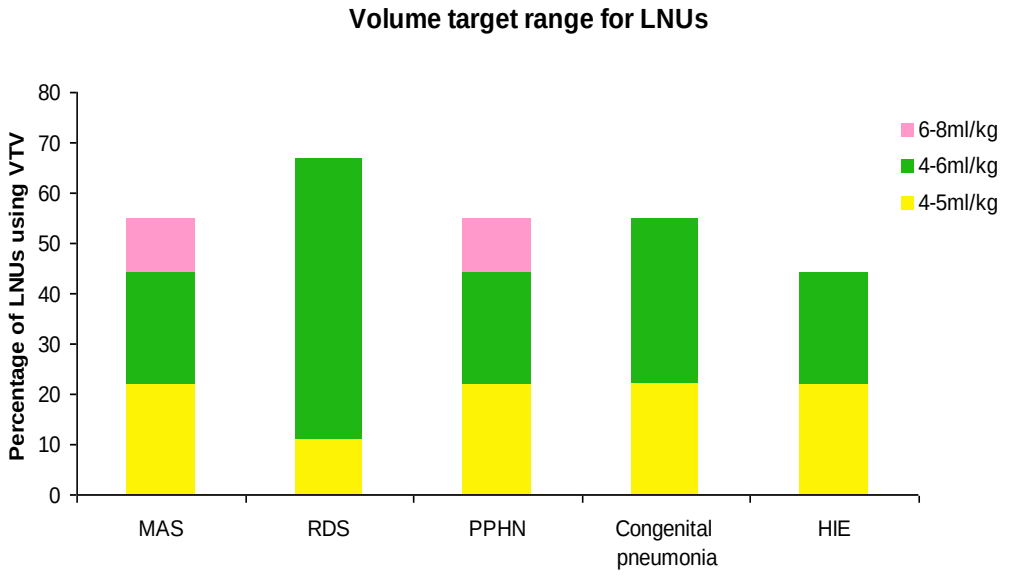


Figure 3.3 Commonly used volume-target ranges in LNUs

3.3.5.2 Maximum Peak Inflation Pressure (PIP)

The majority of NICUs replied they would set the maximum PIP as required, that is, the PIP that would enable delivery of the set tidal volume (Figure 3.4). Amongst LNUs using VTV, a more variable pattern was seen (Figure 3.5).

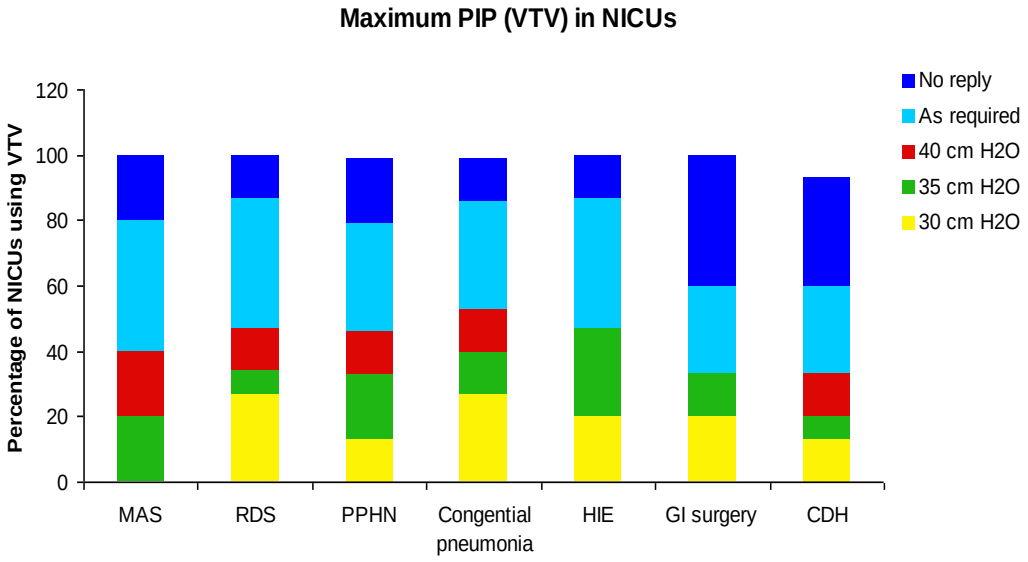


Figure 3.4 Maximum PIP set in NICUs

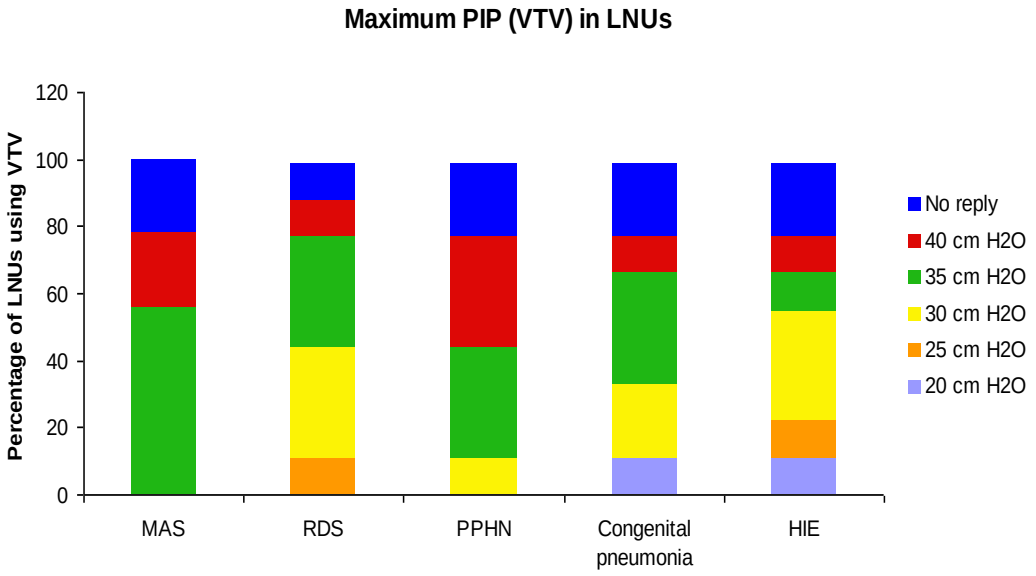


Figure 3.5 Maximum PIP set in LNUs

3.3.5.3 Volume-target (VT) prior to extubation from VTV

For both NICUs and LNUs, the median minimum tidal volume target the infant would be weaned to before extubation was 4ml/kg (range: 3 to 5ml/kg; Figure 3.6)

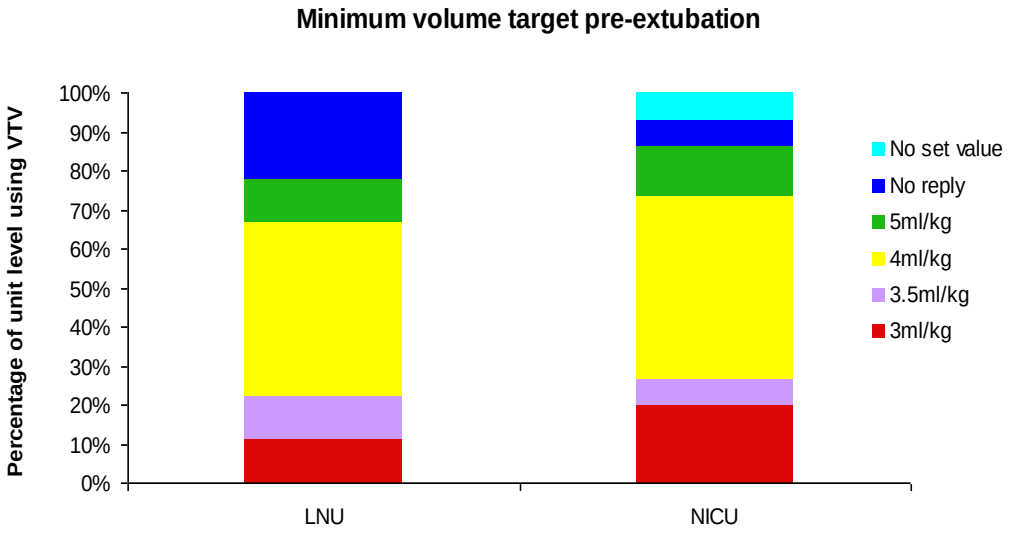


Figure 3.6 Volume-target prior to extubation from VTV

3.3.6 Surfactant therapy

The routine use of surfactant for different pathologies (Figure 3.7) did not differ significantly between different levels of care apart from in RDS, where significantly less use of surfactant was reported by SCUs ($p<0.0001$)..

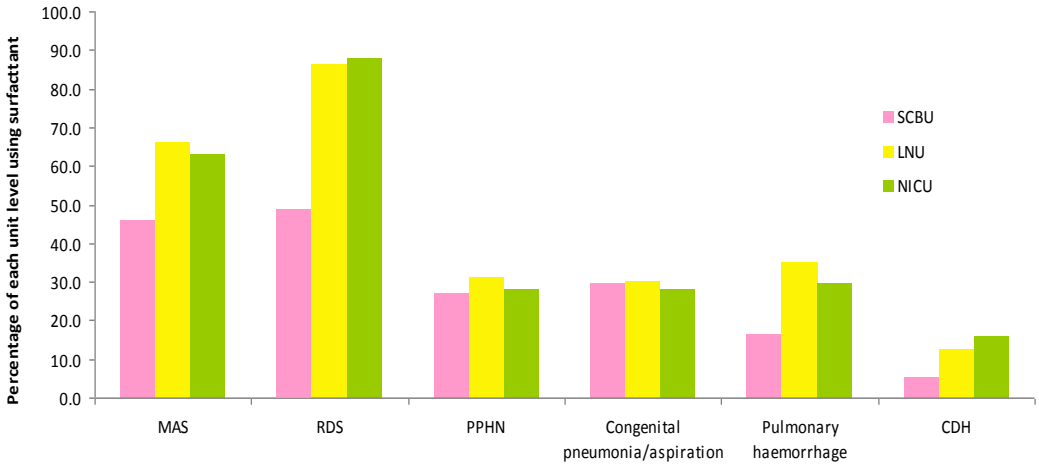


Figure 3.7 Routine use of surfactant in term newborns

3.3.7 Nitric oxide (NO) therapy in term newborns

49 NICUs replied to this question. 55% of responding NICUs started at 20ppm, 25% at 10ppm and 20% at 5ppm. 76% of NICUs used a maximum dose of 20ppm, 20% used 40ppm and 4% used 25 ppm.

3.4 Discussion

These results demonstrate that there was variation in practice with regard to respiratory support of infants born at term requiring mechanical ventilation. In particular, there was significant variation between hospitals providing different levels of neonatal care in part reflecting that in line with the BAPM guidelines (105), SCUs transferred infants requiring rescue respiratory support to a unit providing a higher level of neonatal care. Other variations in

practice, however, occurred between NICUs, for example, different levels of volume targeting or starting dose of NO.

A recent survey reported that 60% of Australasian NICUs and 40% of Scandinavian NICUs routinely use VTV in prematurely born infants (82), perhaps reflecting the positive benefits reported in prematurely born infants in the recent Cochrane review (34). This survey demonstrates that 26% of UK NICUs routinely use VTV in term born infants, although there have been no randomised studies demonstrating similar benefits in term born infants. In term born infants, practitioners used volume target levels from 3 to 10 ml/kg and the median minimum volume target weaned to before extubation was 4ml/kg.

A variety of ventilators were used for both conventional and high frequency oscillatory ventilation. It has previously been shown (81) that during VTV, different ventilators deliver different airway pressure waveforms, whether this influences outcome has not been tested. Oscillator performance also differs (106), the Sensormedics delivers much greater tidal volumes, particularly at lower frequencies. Only 47% of units used the Sensormedics for term born infants indicating that less “powerful” oscillators were being used to support the majority of term born infants. Whether a particular ventilator is more suited to the delivery of a particular mode such as VTV or HFOV in term born infants is unknown.

There is no evidence to support the use of prophylactic and little to support use of rescue HFO in term born infants. A meta-analysis (107) of two RCTs comparing HFOV to conventional ventilation (CV) in term or near-term infants with hypoxic respiratory failure concluded there was no benefit in using

rescue HFOV rather than CV in term or near-term infants with severe respiratory failure. Clark's study (108) did show that significantly more infants who met failure criteria on CV responded to HFOV compared to infants who failed HFOV responding to CV (p=0.03). Despite the paucity of evidence, the results of this survey showed high use of HFOV as initial or rescue mode by NICUs. As infants' respiratory failure improves, infants on HFOV could be switched either to CV for further weaning prior to extubation or be extubated directly from HFOV. There is no evidence to support one method over the other in term infants, interestingly the majority of NICUs changed infants to CV from HFOV for a period prior to extubation.

There is evidence to support surfactant use in certain respiratory conditions in term infants. In MAS in infants born at or near term, a meta-analysis showed that surfactant reduced the risk of requiring extracorporeal membrane oxygenation (ECMO) (RR 0.64, 95% CI 0.46, 0.91) (109). A randomised, multicentre, double-blind, placebo-controlled trial in term infants with severe respiratory failure (MAS, sepsis and idiopathic PPHN) (110) demonstrated administration of surfactant was associated with a significant reduction in the need for ECMO (p=0.038), but no statistically significant difference in the duration of ventilation or the incidence of chronic lung disease. A retrospective observational study (111) of 118 infants with respiratory failure and group B Streptococcal infection, 19% of whom were more than 35 weeks gestation, showed a significant reduction in the median fraction of inspired oxygen (FiO_2) with surfactant treatment (0.84 to 0.5, p<0.01). Observational studies, in mostly prematurely born infants with pulmonary haemorrhage, showed surfactant therapy was associated with

improvements in severity of respiratory failure as assessed by the ventilatory index (VI = FiO_2 x mean airway pressure / PaO_2) (112) and a significant reduction in the mean oxygenation index (113). No benefit, however, has been shown of the surfactant in term infants with congenital diaphragmatic hernia. Indeed, in antenatally diagnosed term born CDH patients, surfactant treatment was associated with a higher use of ECMO (p=0.04) and incidence of chronic lung disease (p=0.0066) and a lower survival (p=0.0033) (114). Inhaled NO reduces incidence of the combined outcome of death or need for ECMO in ventilated, term born infants (115). Studies suggest that the maximal beneficial effect of NO occurs at less than 30ppm (116), as a consequence it has been recommended that the starting dose should be 20 ppm (115). Just over half of the responding NICUs started at the recommended dose of 20ppm, with the remaining NICUs starting at lower, possibly suboptimal doses of 5-10 ppm.

The survey was sent to the lead clinician for each unit, with the questions in the survey asking for the unit's practice. Some responses however could have reflected the respondent's personal views rather than departmental practice. This is a potential drawback of the study.

In conclusion, there is variation in respiratory support practice for term born infants, particularly between units offering different levels of neonatal care. These results emphasize further research is needed to produce evidence-based guidelines for the ventilation of infants born at or near term.

Chapter 4: Study comparing levels of volume-targeting in term born infants

4.1 Introduction

During volume targeted ventilation (VTV) a near-constant tidal volume is delivered, despite even rapid changes in the infant's lung function. The level of volume-targeting influences the infant's work of breathing (WOB) as assessed by measurement of the transdiaphragmatic pressure time product (PTP_{di}) (83, 84). Amongst prematurely born infants, in both acute respiratory distress (83) and during weaning (84), a volume target (VT) level of 6ml/kg compared to 4ml/kg was associated with a significantly lower PTP_{di}. Similar studies have not been undertaken on infants born at or near term. The aims, therefore, of this study were to determine, in infants born at or near term, the impact of different levels of volume-targeting on the WOB and, within the normal tidal volume range, if there was a level that reduced the WOB below that experienced during ventilatory support without volume-targeting.

4.2 Methods

4.2.1 Protocol

Infants more than or equal to 34 weeks in gestation at birth were eligible for inclusion in the study, if they were supported by a time-cycled, pressure-limited ventilator either in a continuous mandatory (CMV) or a triggered mode [assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV)] and making spontaneous respiratory efforts. Infants with a congenital diaphragmatic hernia or severe hypoxic ischaemic encephalopathy were excluded. Infants were entered into the study if their parents gave informed written consent. The study was approved by the King's College Hospital Research Ethics Committee.

All the infants were ventilated using SLE 5000 ventilators (software version 4.3; SLE Ltd., South Croydon, UK). During volume-targeted mode (TTV^{plus}), inflation was terminated once the VT level was achieved, which meant the delivered inflation time could be shorter than the set inflation time. Measurements were only carried out if the infant had blood gases in the normal range (pH 7.25-7.4, $PaCO_2$ 4.5-6.5 kPa). Infants were studied first on their baseline ventilation, that is, without volume-targeting and then studied during three 20 minute periods of VTV with VT levels of 4, 5 and 6 ml/kg delivered in random order. In between each period of VTV, the infants were returned to "baseline" ventilation for 20 minutes (Figure 4.1).

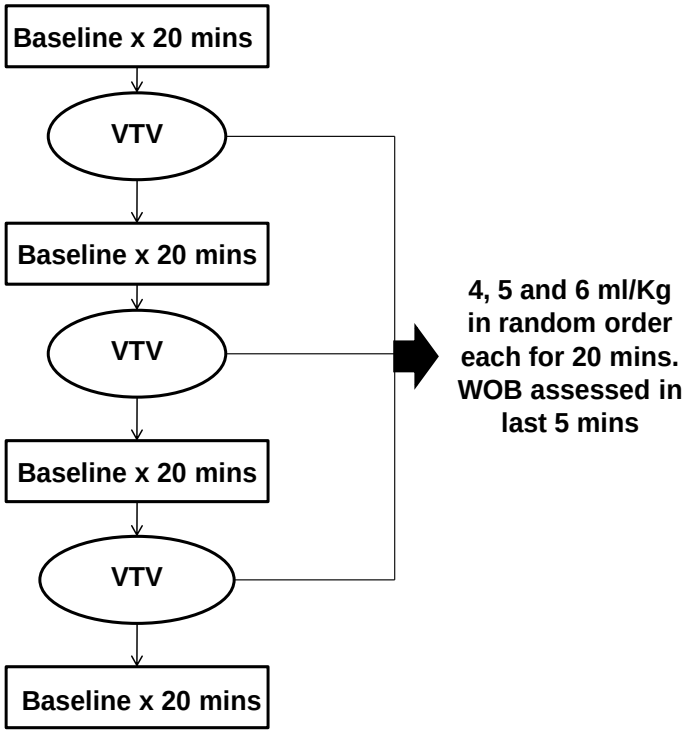


Figure 4.1 Flow diagram of protocol for study on optimal VT level in term and near-term infants

The WOB was assessed by measurements of the transdiaphragmatic pressure (PTP_{di}). The baseline PTP_{di} was calculated by averaging the PTP_{di} at the four baseline periods. At each step, the mean expiratory tidal volume (VT_e) of the ventilator breaths delivered during the period for which PTP_{di} was calculated and the mean peak inflation pressure during the same period were determined. Each infant's spontaneous respiratory rate was calculated for the period from which PTP_{di} was derived at each VT level and the total expiratory minute volume (infant plus ventilator) determined.

4.2.2. Sample Size

Recruitment of sixteen infants allowed detection of a difference in the PTP_{di} results equivalent to one standard deviation with 80% power at the 5% level.

4.2.3 Statistical analysis

Differences were assessed for statistical significance using Friedman's test with Dunn's multiple comparison test. GraphPad Prism 5.0 (GraphPad, La Jolla, CA) was used.

4.3 Results

Sixteen infants with a median gestation at birth of 38 (range 34-41) weeks and birth weight of 3.1 (range 1.5-4.1) kg were studied at a median postnatal age of 5 (range 2-17) days. Five infants were supported by CMV, eight by SIMV and three by ACV. Two infants had meconium aspiration syndrome, two persistent pulmonary hypertension of the newborn, two respiratory distress syndrome, nine infants had surgical conditions (five gastroschisis, two exomphalos major, two bowel obstruction) and one infant had moderate perinatal asphyxia following shoulder dystocia at delivery. At baseline, the

infants were receiving a median peak inflating pressure (PIP) of 16 (14-21) cm H_2O, PEEP of 5 (4-5) cm H_2O, inflation time (T_i) of 0.4 (0.34-0.5) seconds and an inspired oxygen fraction (FiO_2) of 0.21 (0.21-0.3). All the infants were ventilated via shouldered ET tubes which have minimal or no leak (117). Ten infants were receiving morphine as an intravenous infusion of between 5 and 10 micrograms/kg/hour at the time of the study.

One infant with bowel obstruction studied post-operatively had a prolonged period of apnoea while receiving a VT level of 6ml/kg. A capillary blood gas revealed a $PaCO_2$ of 4.0 kPa. Due to the lack of spontaneous respiratory effort, it was not possible to measure his PTP_{di} at a level of 6ml/kg, thus this infant's data were excluded from the analysis. At a VT level of 4ml/kg, four infants were making vigorous respiratory efforts and demonstrated they were receiving no ventilator inflations. The ventilator display, however, indicated the infants were receiving PIPs between 7 to 9 cmH_2O, which were active expiratory efforts by the infants. An *in vitro* experiment to investigate increased spontaneous infant effort leading to lack of ventilator support at low tidal volume targets in VTV on the SLE 5000 ventilator, a phenomenon observed both while the study was being carried out as well on subsequent analysis of the traces. In this experiment, a syringe was used to mimic a mechanically ventilated term born infant's spontaneous respiratory activity, generating tidal volumes of 20ml with the tidal volume target set at 10ml on the ventilator. This resulted in airway pressure deflections which, on analysis, revealed that the positive pressure (PIP) readings on the ventilator panel were actually corresponding to 'expiratory efforts' simulated by the pushing of the piston of the syringe. It was concluded that no inflation pressure was

being delivered by the ventilator. Inflation pressures were recorded as zero for the four infants in which this finding was observed.

The mean PTP_{di} was higher at a VT level of 4ml/kg than at 5ml/kg ($p<0.01$) and 6ml/kg ($p<0.001$). The mean PTP_{di} was only below that at baseline at a VT level of 6ml/kg ($p<0.01$) (Table 4.1; Figure 4.2).

The median PIP was significantly lower at VT levels of 4ml/Kg than at both VT levels of 5ml/kg ($p<0.05$) and 6ml/kg as well as baseline ($p<0.001$) (Table 4.3). The median VT_e was significantly higher at a VT level of 4 compared to 5ml/kg ($p<0.05$). The inflation time was lower at 4ml/kg than at baseline ($p<0.05$). The minute volume did not differ significantly between the baseline and any of the VT levels.

	Baseline	**4ml/kg**	**5ml/kg**	**6ml/kg**
Overall (n=15)	256 (133-419) [c]	310 (194-487) [a,b]	232 (110-433) [a]	163 (54-377) [b,c]
CMV (n=4)	229 (159-354)	332 (260-487)	177 (129-312)	157 (116-186)
SIMV (n=8)	256 (133-419)	289 (194-428)	242 (131-433)	200 (54-377)
ACV (n=3)	285 (156-355)	319 (216-478)	138 (110-252)	128 (117-252)

Table 4.1 PTP_{di} ($cmH_2O.s/min$) related to VT levels.

Results displayed as median (range). [a, c] $p<0.01$; [b] $p<0.001$

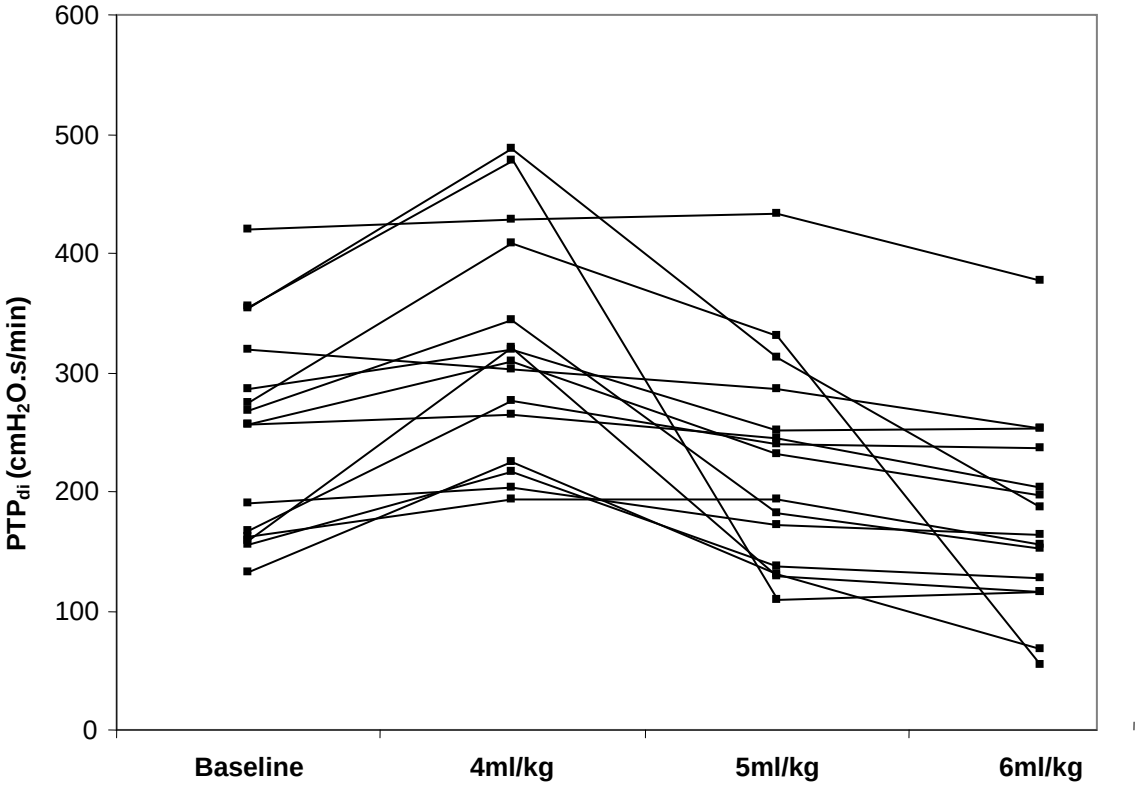


Figure 4.2 PTP_{di} results with individual infant's results shown as linked data points. Results at baseline are the average of four baseline periods.

	Baseline	4 ml/kg	5 ml/kg	6 ml/kg
PIP (cmH_2O)	16 [a] (14-21)	8 [a,b,c] (0-14)	13 [b] (7-20)	17 [c] (8-21)
VT_e (ml/kg)	6.4 [d] (3.2-11)	5.0 [d,e] (0-9.9)	5.8 (3-8.5)	6.5 [e] (3.4-11.8)
T_i (sec)	0.4 [f] (0.34-0.5)	0.33 [f] (0.25-0.41)	0.35 (0.27-0.41)	0.35 (0.27-0.41)
Infant RR (breaths/min)	65 (45-83)	66 (36-90)	60 (48-78)	60 (36-96)
Minute volume (ml/kg/min)	326 (189-858)	339 (205-1030)	329 (198-608)	321 (209-726)

Table 4.2 Peak inspiratory pressure (PIP), expiratory tidal volume (VT_e), inflation time (Ti), infant spontaneous respiratory rate (RR) and total minute volume related to VT level.

Results are displayed as median (range).

[a, c] $p<0.001$; [b,d,e,f] $p < 0.05$

4.4 Discussion

The WOB in at or near term infants was significantly higher at a VT level of 4ml/kg compared to both VT levels of 5ml/kg and 6ml/kg. Only a VT level of 6ml/kg was associated with a significantly lower WOB compared to baseline, that is, ventilatory support without volume-targeting. The infants were receiving CMV or a triggered mode. The numbers on each ventilator mode are too small for subgroup analysis, but the data in the table (Table 4.1) shows a similar trend in PTP_{di} levels with increasing VT levels for all three ventilator modes.

Infants were studied at VT levels within the tidal volume range, that is, 4 to 6ml/kg. The infants studied required relatively low levels of ventilatory support as indicated by a maximum peak inflation pressure of 21 cmH_2O and thus were likely to have mild respiratory failure. Thus, we did not use VT levels above 6ml/kg, as, although these may have further reduced the WOB, their use might have resulted in volutrauma or hypocarbia. Indeed, one infant had a prolonged period of apnoea at a VT level of 6ml/kg and the $PaCO_2$ level was 4 kPa.

The infants were ventilated using the SLE 5000, which during VTV terminates inflation short of the preset inflation time if the volume had already been delivered. This, however, did not affect our results, as we used the same ventilator to compare the VT levels. At a VT level of 4ml/kg, however, certain of the infants received an inflation time of less than 0.3 seconds and the inflation time was significantly shorter than at baseline. Our finding that at a VT level of 4ml/kg four infants had no inflations delivered as they were making very vigorous efforts, further suggests this low level of VT should not be used in near term or term born infants. Interestingly, though the ventilator display recorded peak inflating pressures in those infants, these pressures were actually generated by the infants actively expiring. We would suggest infants should be extubated from VT levels of at least 5ml/kg.

Regardless of the VT level, the minute volume did not differ significantly. The infants' respiratory rates also did not differ significantly between VT levels. Those results indicate that the infant compensated for the reduced support from the ventilator by increasing the depth of their respiratory efforts and tidal volume exchange (Table 4.2) and hence their WOB was increased.

In conclusion, we have demonstrated that VT levels of 4ml/kg compared to higher levels of VT are associated with an increased WOB in at or near term born infants with a variety of diagnoses. A VT level of 6ml/kg was associated with a reduction in the WOB below baseline, but was associated with hypocarbia in one infant. We conclude higher rather than lower levels of VT within the normal tidal volume range should be used, but it is important to monitor blood gases to avoid hypocarbia.

Chapter 5: Study comparing volume-targeted to pressure-limited ventilation in prematurely born infants

5.1 Introduction

During volume-targeted ventilation (VTV), a constant volume is delivered with each ventilator inflation regardless of changes in the infant's lung function. In Chapter 4 it was demonstrated that in the short term, the work of breathing (WOB) was reduced during VTV if higher rather than lower levels of volume-targeting were used. Increasing the level of respiratory support by increasing the level of volume-targeting, however, could unfavourably impact on respiratory muscle strength. The aim of this study was to determine in a randomised study of prematurely born infants with acute respiratory distress, whether VTV compared to pressure-limited ventilation (PLV) using the same ventilator type was associated with a shorter time to reach weaning criteria. In addition, the study was designed to assess if any difference in the time to reach weaning criteria was associated with differences in the WOB or respiratory muscle strength between the two groups. A secondary aim of the study was to determine if VTV was associated with less hypocarbia compared to PLV.

5.2 Methods

5.2.1 Protocol

A randomised trial was carried out at King's College Hospital NHS Foundation Trust between August 2010 and February 2012. Infants born at less than 34 weeks of gestational age who were mechanically ventilated in the first week after birth were eligible for entry into the trial. Infants with major congenital anomalies, those who had been ventilated for more than 24 hours and/or were supported by high frequency oscillatory ventilation (HFOV) were

ineligible for this study. Infants were enrolled into the study if their parents gave informed written consent. The study was approved by King's College Hospital Research Ethics Committee.

Patients were randomised using sequential opaque sealed envelopes and random number table generation to receive either VTV or PLV. The infants in both arms of the trial were supported by SLE 5000 ventilators (Software version 4.3; SLE Ltd, South Croydon, UK). At randomisation, no changes were made to the ventilator settings of those infants who were to receive PLV. For those randomised to VTV, the only changes made were to set the VT level at 5ml/kg with the leak compensation at 20% and to set a maximum PIP that allowed a delivery of 5 ml/kg. A VT of 5ml/kg was used, as a VT of at least 5ml/kg has been shown in prematurely born infants to be associated with a lower WOB than a VT level of 4ml/kg (83). During VTV with a SLE 5000 ventilator, the maximum set peak inspiratory pressure was delivered to the infant only if the VT level was not achieved. In addition, with the SLE 5000 ventilator, inflation is terminated once the VT level was achieved, which meant that the delivered inflation time might be shorter than the preset inflation time. In this study, if the delivered inflation time was less than 0.2 seconds, then the waveform was altered to give a shallower upstroke to the inflating pressure, prolonging the inflation time. If infants developed a respiratory acidosis on VTV, the VT level was increased in steps of 0.5ml/kg to a maximum of 6ml/kg. If infants developed a respiratory acidosis on PLV, the rate was increased in steps of 5 breaths per minute to a maximum of 60 breaths per minute and if necessary the pressure was increased. If those manoeuvres did not bring about the desired improvement in the blood gases,

the infant was transferred to HFOV. Infants were deemed to have failed the randomised mode if they required HFOV or a peak inflation pressure greater than 26 cmH_2O or had a pulmonary haemorrhage.

The primary endpoint was the time to reaching weaning criteria. Weaning criteria was defined in the PLV arm as a peak inflation pressure (PIP) of ≤ 16 cmH_2O and a fraction of inspired oxygen (FiO_2) of ≤ 0.4. In the VTV arm, weaning criteria was defined as a VT level of 5 ml/kg with PIP ≤ 16 cmH_2O. Those settings had to have been maintained or weaned further over the subsequent six hour period. Once the infants reached weaning criteria, caffeine was administered. In the PLV arm infants followed the unit's routine practice prior to extubation, that is the infant switched to assist control ventilation (ACV); SIMV was only used if the infant was hypocarbic on ACV despite reduction in pressures but not deemed ready for extubation. In the VTV arm, infants were also switched to ACV/SIMV but with the intention of volume-targeting also being used. Throughout the study and during ongoing ventilation, the policy was to keep the pCO_2 in the following ranges:

4.5-5.5 kPa on days 1-2 after birth;

5-7 kPa on days 3-7 after birth

with the arterial pH between 7.25 and 7.35.

After day seven permissive hypercarbia was permitted providing the pH remained above 7.25 on arterial or capillary blood gas assessments.

An episode of hypocarbia was defined as a pCO_2 less than 4.5 kPa on any blood gas measurement during the first 72 hours after birth. The number of arterial blood gases obtained in that time period was recorded.

Measurements of the WOB and respiratory muscle strength were planned for 24 and 48 hours after randomisation on the randomised modes of ventilation and immediately prior to extubation. The WOB was assessed over a five minute period on each occasion by measurement of the transdiaphragmatic pressure time product (PTP_{di}) as previously described. Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure (Pimax) and maximum expiratory pressure (Pemax) generated during an airway occlusion during crying. The clinicians caring for the infants were blinded to the results of the physiological measurements.

The nurses recorded the level of respiratory support hourly on observation charts. The infants' demographics and the levels of respiratory support at randomisation and pre-extubation were determined from the medical records and the intensive care observation charts. The duration of ventilation was the time from randomisation to successful extubation, that is when the infant remained extubated for at least 48 hours. The indications for reintubation were the development of a respiratory acidosis (pH < 7.25) which persisted for more than four hours, the occurrence of frequent apnoeas or one major apnoea and/or an increased oxygen requirement ($FiO_2 \geq 0.6$).

5.2.2 Sample size

Using results from prematurely born infants previously ventilated on the unit, we calculated that recruitment of 40 infants allowed detection of a difference between the groups in the time to achieve predefined weaning criteria of 72 hours with 90% power at the 5% level. In addition, that sample size allowed us to detect a difference in the results of the physiological measurements equivalent to one standard deviation with 80% power at the 5% level.

5.2.3 Statistical analysis

The analysis was conducted on an intention-to-treat basis. Outcome data were analysed using Cox regression since there was censoring of the primary outcome, that is, the time to achieve weaning criteria. Results are given as hazard ratios with 95% confidence intervals (CIs). In addition, the Cox model was used to estimate the median time to weaning by ventilation group. The results of the physiological measurements were slightly skewed, but transformations did not correct and so they were analysed using t tests but as a sensitivity analysis, tests were also done using the Mann Whitney U test. Binary outcomes were analysed using chi-squared or Fisher's exact tests as appropriate. All analyses were conducted using Stata v11.

5.3 Results

There were 93 eligible infants during the study period (Figure 5.1). The recruited infants were of a lower gestational age than the non-recruited infants (median 27 weeks, range 23-34 weeks versus 29 weeks range 24-34 weeks respectively) p = 0.022 and were of lower birth weight (median 916g, range 500-2122g versus 1190g, range 545-2526g respectively) p = 0.014. There was no evidence of imbalance in the demographic data of the infants randomised to the PLV or VTV group (Table 5.1). When the infants reached weaning criteria, 18 infants in the VTV arm were switched to ACV (15 with volume targeting) one to SIMV and one infant died before extubation. The ventilator settings immediately after randomisation were similar in the two groups (Table 5.1). In only two infants it was necessary to increase the VT level above 5ml/kg because the infants developed a respiratory acidosis.

There were no significant differences in the time to achieving weaning criteria median 14 hours (VTV) versus 23 hours (PLV); hazard ratio = 0.82 (95% CI 0.42, 1.58, p = 0.055) (Figure 5.2), the time to successful extubation or the number of infants in each group who met failure criteria (Table 5.2). The ventilator settings at extubation were similar in the two groups (Table 5.2). For logistical reasons and that the majority of infants reached weaning criteria prior to 24 hours after randomisation few infants had measurements at 24 and 48 hours (n=7, n=4 respectively) and thus those results are not reported. There were no significant differences between the two groups in the median PTP_{di}, Pimax or Pemax results pre-extubation (Table 5.3). The only significant difference in other outcomes was that fewer infants in the VTV compared to the PLV arm had episodes of hypocarbia (8 versus 19, p<0.001) (Table 5.4). The number of blood gases obtained in the first 72 hours after birth was similar in each group (Table 5.4).

5.4 Discussion

The study has demonstrated that there was no significant difference in the time to reach weaning criteria in prematurely born infants with acute respiratory distress supported by PLV or VTV. The time to reach weaning criteria was chosen as the primary outcome as we wished to determine whether VTV compared to PLV had favourable effects during the period when the infants had acute respiratory distress. Our sample size allowed us to detect a difference in the time to reach weaning criteria of 72 hours (with 90% power), but unexpectedly the majority of infants in both groups met the weaning criteria within 72 hours. Our sample size, however, was also powered to detect a difference in the results of the physiological

measurements equivalent to one standard deviation and we demonstrated no significant differences in the pre-extubation WOB or respiratory muscle strength results. Those measurements were made when the infants had been transferred to ACV/SIMV for weaning from ventilatory support, but the majority in the VTV arm remained additionally on volume-targeting. Our results then reflect that a combination of PLV and ACV/SIMV was associated with similar levels of WOB and respiratory muscle strength as a combination of VTV and ACV/SIMV with volume targeting.

Our data suggest that VTV as used in this study and PLV provide similar levels of respiratory support to prematurely born infants with acute respiratory distress. Indeed, immediately after randomisation, the peak inflation pressure and inflation times did not differ between the two groups. We used a VT level of 5ml/kg and it is possible if we had used a higher level, we may have had different results. In a previous study, however, a VT level of 6ml/kg was not associated with a WOB that was significantly less than at baseline, ie no VT (83). We were reluctant to use a higher VT level than 6 ml/kg as studies in prematurely born lambs have shown “dose”-dependent lung damage with increasing volume delivery (118). In addition, although a wide range of VT levels were used in the studies included in the meta-analysis (34), the most common VT level used was 5ml/kg. Only two infants required an increase in VT levels above 5ml/kg because they developed a respiratory acidosis further suggesting that a VT level of 5ml/kg was appropriate.

In the meta-analysis reported in the Cochrane database, the duration of ventilation was shorter in the VTV arm. In this RCT, the median duration of ventilation was twice that in the PLV compared to the VTV arm. Of note, the

ventilator settings immediately prior to extubation were similar and thus the clinicians had not biased the results by extubating the VTV group “sooner”. It should be noted, however, that this difference was not statistically significant and our sample size was not calculated to detect a difference in the duration of ventilation.

The secondary outcomes of PDA, pneumothorax, IVH ≥ grade 3, cystic PVL and BPD are reported only to give the reader more information regarding the population we studied. The episodes of hypocarbia did differ significantly between the two groups. This seems unlikely to be by chance given the level of significance and the limited number of secondary outcomes. In addition, the number of blood gases obtained during the first 72 hours did not differ significantly between the two groups, so the difference in the number of episodes of hypocarbia was genuine. This is an important finding, as hypocarbia in prematurely born infants is significantly associated with the development of PVL and adverse neurodevelopmental outcomes (36, 37). Thus, despite finding no difference in our primary outcome, we would recommend VTV in prematurely born infants with acute respiratory distress as a means of reducing hypocarbia.

Our study has a number of strengths and some limitations. The same ventilator type was used in both arms of the study; performance has been shown to differ according to type of ventilator with regard to airway pressure waveforms (81). We recruited consecutive infants who fulfilled the eligibility criteria and a researcher was available. The recruited and non-recruited infants, however, differed significantly in that those who were not recruited were significantly more mature and of greater birth weight. Their non-

recruitment likely reflects that such infants frequently require a shorter duration of ventilation and hence there would be less time to inform the researcher and they might achieve the primary outcome/extubation before consent can be taken. In addition, parents may have been less likely to consent to a ventilation study of acute respiratory distress if their infant's respiratory status was rapidly improving. We emphasize then that our results apply to very prematurely born infants. There were no significant differences in the peak inflating pressures and inflation times or inspired oxygen concentrations between the two groups either immediately following randomisation or pre-extubation. Those results were from the nursing observation charts rather than analysis of continuous electronic recordings. The nurses, however, made the recordings according to the unit's policy, that is, they made the observations at hourly intervals. It thus seems unlikely they would have biased the results. The clinicians were not blinded to the intervention and indeed were not in any of the studies included in the meta-analysis, as carrying out a blinded ventilation study is difficult and would require additional staff. The lack of significant differences in most of our results would suggest that the lack of blinding had not influenced performance of the study.

In conclusion, in prematurely born infants with acute respiratory distress, VTV compared to PLV did not improve the time to reach weaning criteria or the results of physiological assessments. The significant reduction in episodes of hypocarbia in the VTV versus the PLV group suggests VTV might improve long term outcome. That hypothesis needs to be assessed in an appropriately-sized randomised controlled trial.

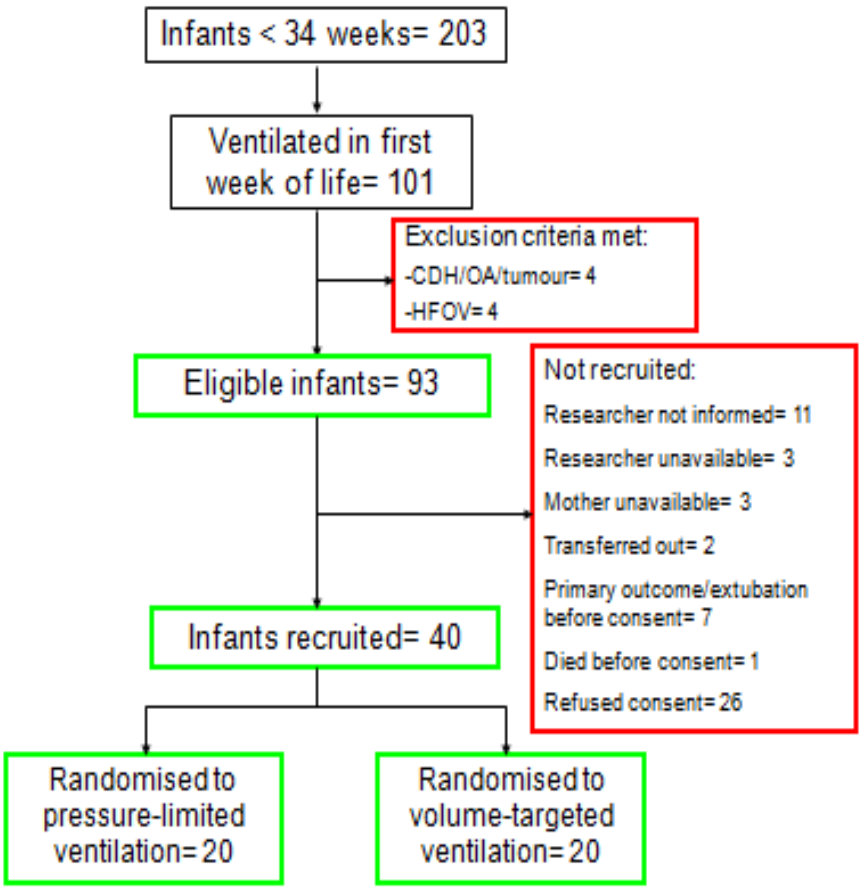


Figure 5.1 Consort diagram depicting recruitment

	PLV n=20	**VTV n=20**	**p value**
Gestational age (weeks)	26 (24-33)	28 (23-34)	0.19
Birth weight (g)	856 (570-2122)	1016 (550-2120)	0.14
Male (n)	11 (55%)	10 (50%)	1.00
Complete antenatal steroids (n)	11 (55%)	14 (70%)	0.51
Age at randomisation (hr)	4 (0.3-10)	5 (1-21)	0.38
At randomisation:			
PIP (cm H_2O)	20 (17-23)	20 (16-24)	0.77
Inflation time (s)	0.37 (0.34-0.4)	0.36 (0.34-0.4)	0.85
FiO_2	0.31 (0.21-0.62)	0.33 (0.21-0.70)	0.41

Table 5.1 Demographics by mode of ventilation.

Data are presented as median (range) or n (%).

	PLV n=20	VTV n=20	p value
Time to achieve weaning criteria (hr)	23 (6 - 1679)	14 (1-1138)	0.55
Met failure criteria: Causes: Required HFOV Pulmonary haemorrhage	3 3 0	5 3 2	0.69
Failed first extubation	6	3	0.45
Duration of ventilation (hr)	114 (6-1696)	49 (1-1206)	0.18
At extubation: PIP (cm H_2O) Inflation time (s) FiO_2	 15 (9-16) 0.35 (0.32-0.38) 0.24 (0.21-0.42)	 14 (6-17) 0.36 (0.34-0.38) 0.23 (0.21-0.40)	 0.38 0.20 0.83

Table 5.2 Outcomes by ventilation mode.

Data expressed as median (range) or n

	PLV	VTV	p value
PTP_{di}	162.30 (77-295), 8	205.80 (74-225), 7	0.61
Pi_{max}	38.1(5.7-64.9), 11	38.9 (15.6-58.0), 8	0.97
Pe_{max}	14.5 (7.4-35.4), 10	17.7 (4.2-45.6), 8	0.89

Table 5.3 Results of the physiological measurements pre-extubation by ventilation mode. Data shown as median (range) and the number of infants for whom results were available.

	PLV n=20	VTV n=20	p value
Episodes of hypocarbia in the first 72 hr	19	8	<0.001
Number of blood gases in the first 72 hr	17 (5-29)	16 (4-30)	0.55
PDA treated with Ibuprofen	7	2	0.13
PDA ligation	2	1	1.00
Pneumothorax	0	2	0.23
IVH≥ grade 3	3	0	0.23
Cystic PVL	0	1	1.00
Postnatal steroids	2	2	1.00
Oxygen dependency at 28 days	14	11	0.30

Table 5.4 Other outcomes

Data presented as number of infants affected.

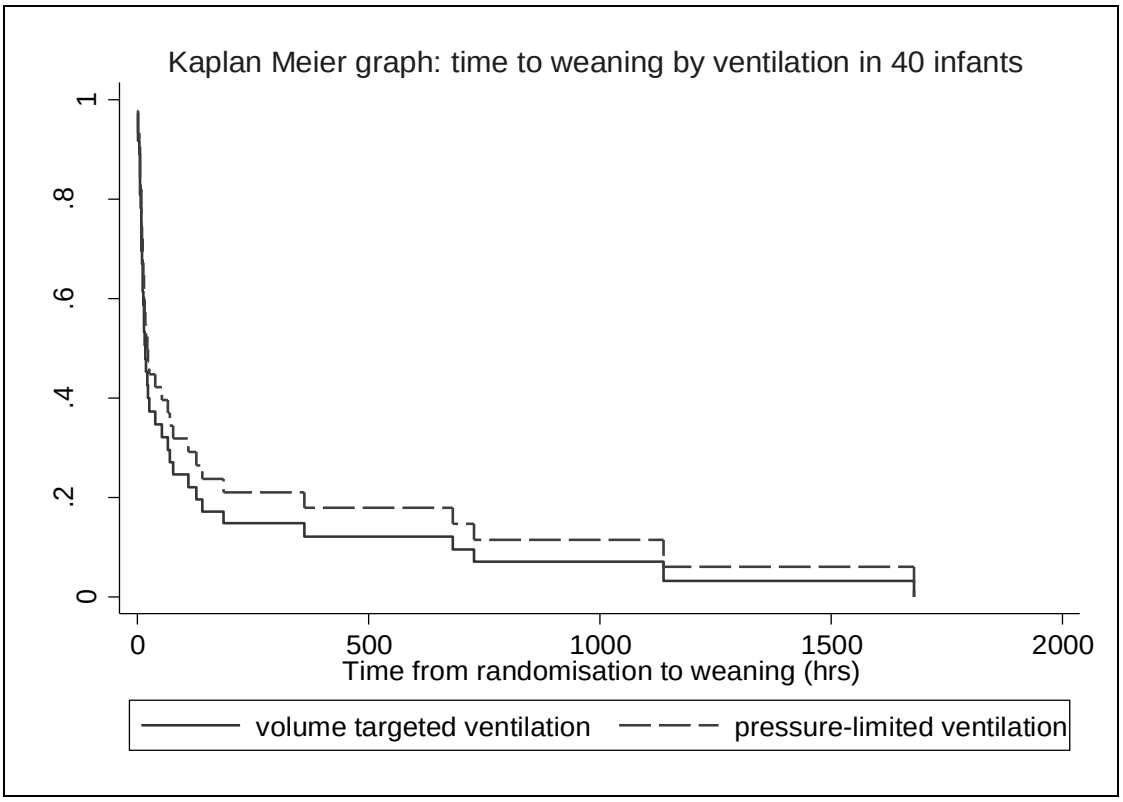


Figure 5.2 Kaplan Meier curve for the time from randomisation to meet weaning criteria

Chapter 6: Patient-ventilator interactions in term born infants

6.1 Introduction

Neonates often breathe while being mechanically ventilated. There is very little in the current literature on optimisation of ventilation using patient-ventilator interactions as an outcome. During analysis of recordings measuring work of breathing in term-born infants for this thesis, it became evident from visual inspection of the traces that there existed definite interactions of the type described by Greenough et al in ventilated preterm infants in the 1980s (31, 119). This study describes and classifies spontaneous respiratory efforts in mechanically ventilated infants born at or near term. Comparisons are made between non-triggered and triggered modes on PLV and on VTV at different volume-target levels to determine if there were significantly less asynchronous interactions in any group.

6.2 Methods

6.2.1 Protocol

Data were examined from recordings taken for the primary purpose of measuring the work of breathing. These recordings provided a graphical representation of airway pressure, flow, oesophageal and gastric pressures which could be visually analysed to describe and classify patient-ventilator interactions. Recordings from periods during which infants were receiving time-cycled, pressure-limited ventilation on CMV or SIMV or different levels of volume targeted ventilation were examined. Each infant had at least 20 minutes of recordings from which the first section of trace free of peristaltic artefact was chosen which had one hundred consecutive spontaneous breaths. For comparison at different levels of volume-targeting, fifty

consecutive breaths at each level of volume-targeting were analysed. This was because at 4ml/kg, the pressure delivered by the ventilator was sometimes minimal, making it difficult to distinguish the presence of a mechanical breath.

All infants were studied in the supine position, spontaneously breathing while ventilated, but on variable levels of sedation, ranging from none to 10 micrograms/kg/hr of morphine sulphate as an intravenous infusion. Ventilator settings were determined by the clinical team caring for the infants and not changed by the researcher.

The start and end of inspiration and expiration were determined by visual inspection of the flow trace. Inspiration started and expiration ended at the point when flow crossed zero and became positive, and inspiration ended and expiration started at the point when flow crossed zero and became negative. The change in flow could be brought about either by the ventilator (passive) or the baby (active). This could be determined by determining the temporal relationship of changes in the airway pressure trace reflecting mechanical ventilator cycles, to the oesophageal pressure trace reflecting spontaneous infant effort.

6.2.2 Patterns of patient-ventilator interaction

Five patterns of patient-ventilator interaction were delineated – synchronous, active expiration, prolongation of expiration, augmented inspiration and apnoea.

6.2.2.1 Synchronous inspiration

Synchronous inspiration (Figure 6.1) constituted a pattern where spontaneous inspiration coincided with the mechanical inflation, with no alteration of ventilator flow. The start of the mechanical inflation, represented by the upward deflection of the pressure waveform, coincided with the negative deflection of the oesophageal pressure waveform which represented the start of spontaneous inspiratory effort. During the inflation, the flow waveform remains positive as there is no opposition to inspiratory flow. A small and positive gastric pressure deflection may also be noted, which accompanied the negative oesophageal deflection during a spontaneous infant inspiratory effort.

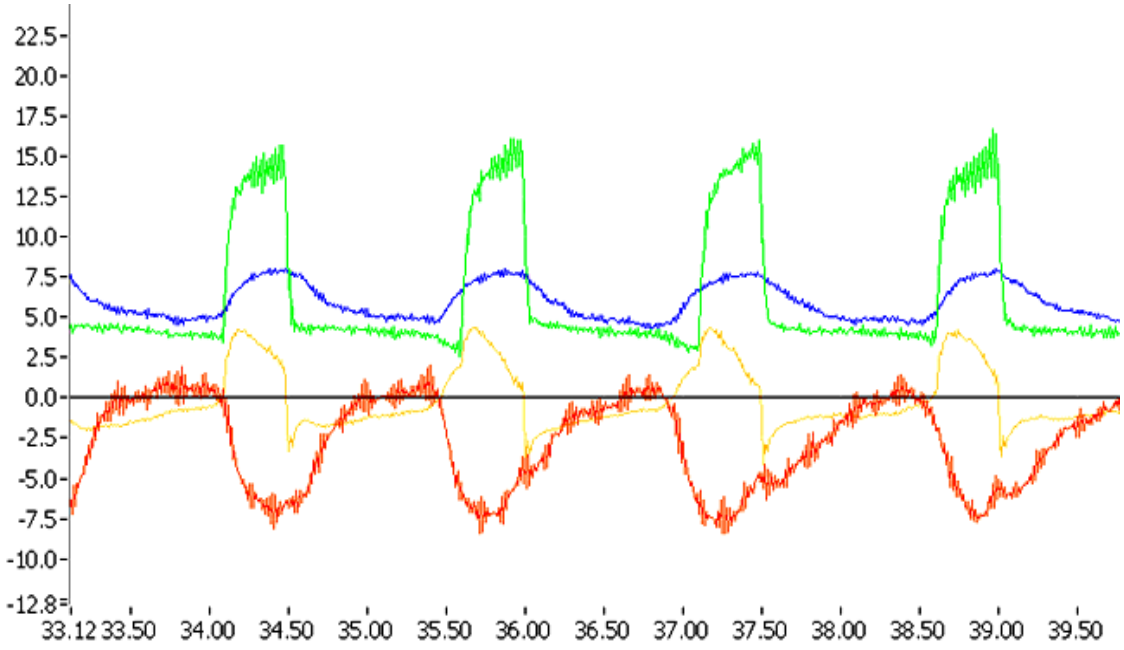


Figure 6.1 Synchronous inspiration

__ **Green** line represents airway pressure

__ **Red** line represents oesophageal pressure

__ **Blue** line represents gastric pressure

__ **Orange** line represents flow

6.2.2.2 Active expiration

Active expiration (Figure 6.2) was a pattern of patient-ventilator interaction where the infant's expiratory effort against the ventilator inflation brought flow to zero or reversed flow during the inflation. During the inflation, there was a positive deflection in the oesophageal pressure waveform, as well as the gastric pressure waveform, representing the infant's active expiratory effort. The effort against the inflations delivered by the ventilator reversed the direction of gas flow, resulting in no flow or an expiratory flow pattern during inflation.

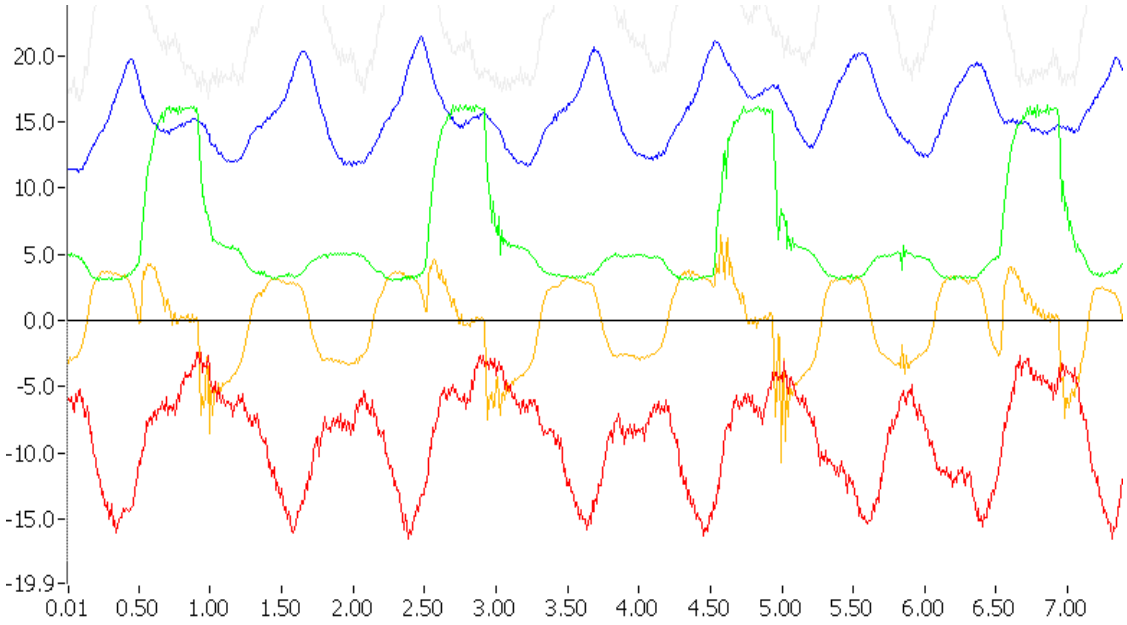


Figure 6.2 Active expiration

__ **Green** line represents airway pressure

__ **Red** line represents oesophageal pressure

__ **Blue** line represents gastric pressure

__ **Orange** line represents flow

6.2.2.3 Prolongation of expiration

In this pattern, the mechanical inflation was associated with prolongation of passive expiration (Figure 6.3). Expiration was classified as passive as the inspiratory flow generated by inflation was not affected. The small positive gastric pressure deflections were probably associated with the rise in intra-abdominal pressure secondary to lung inflation.

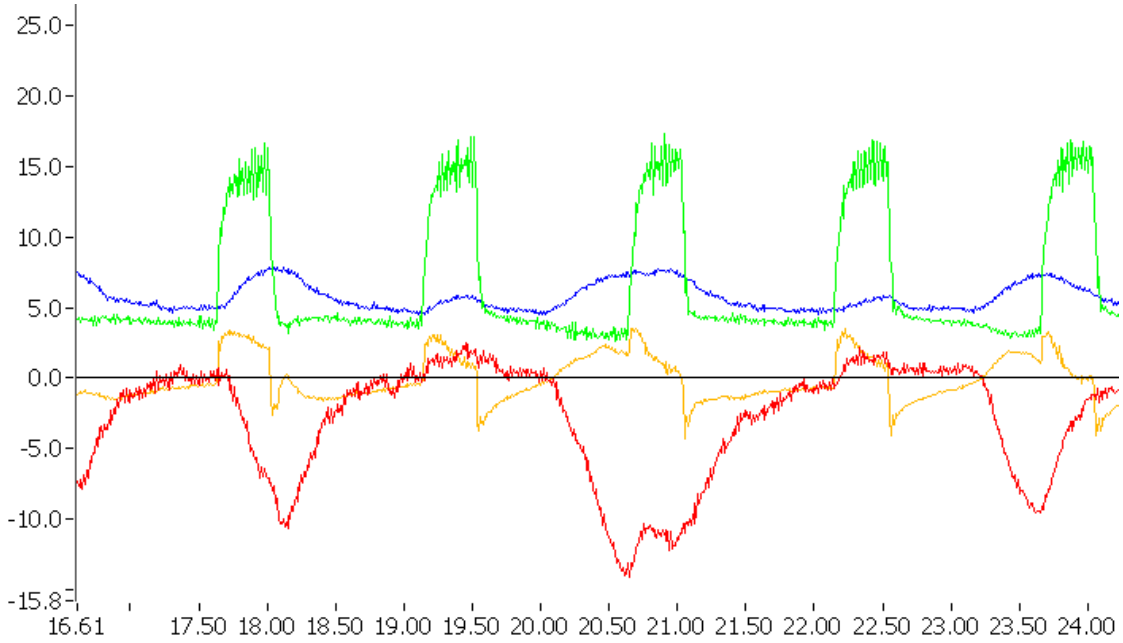


Figure 6.3 Prolongation of expiration

__ **Green** line represents airway pressure

__ **Red** line represents oesophageal pressure

__ **Blue** line represents gastric pressure

__ **Orange** line represents flow

6.2.2.4 Augmented inspiration

This pattern consisted of pronounced inspiratory efforts coincident with inflations (Figure 6.4). The augmented inspirations were characterised by large negative deflections in oesophageal pressure with an accompanying sharp rise in gastric pressure, denoting a forceful inspiratory effort.

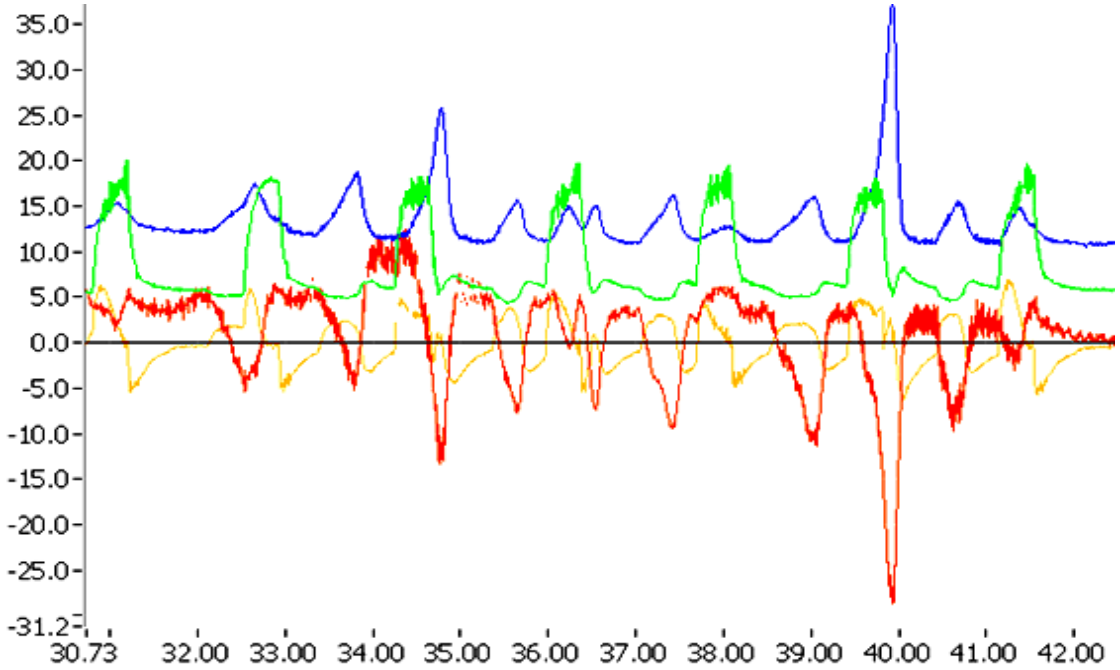


Figure 6.4 Augmented inspiration

__ **Green** line represents airway pressure

__ **Red** line represents oesophageal pressure

__ **Blue** line represents gastric pressure

__ **Orange** line represents flow

6.2.2.5 Apnoea

Apnoea was said to occur when there was no evidence of spontaneous inspiratory or active expiratory effort by the ventilated infant (Figure 6.5). Small elevations in both oesophageal and gastric pressures were seen to occur coincident with the inflation, as a result of the increase in intra-abdominal and intrapleural pressures during lung inflation occurring in the absence of diaphragmatic contraction.

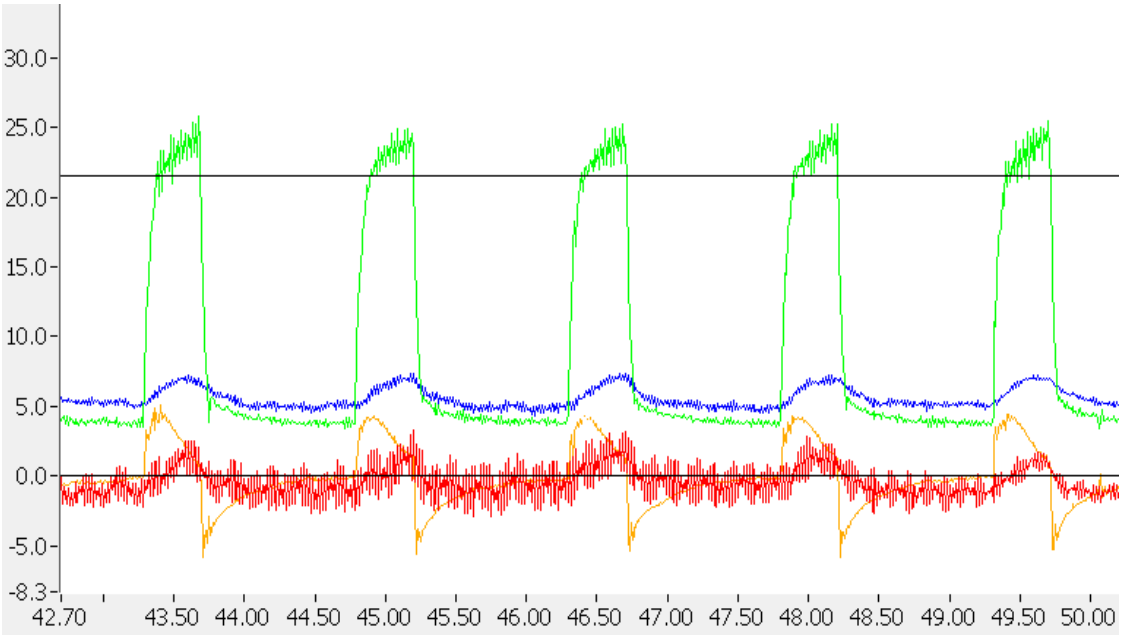


Figure 6.5 Apnoea

__ **Green** line represents airway pressure

__ **Red** line represents oesophageal pressure

__ **Blue** line represents gastric pressure

__ **Orange** line represents flow

6.2.3 Statistical analysis

Differences were assessed for statistical significance using the Chi-squared test. Statistical analysis was carried out with GraphPad Prism 5.0 (GraphPad, La Jolla, CA).

6.3 Results

6.3.1 Comparison of interactions on CMV and SIMV

Twelve infants with a median gestational age of 38 weeks and a median birthweight of 3.1 kg were studied at a median postnatal age of five days. Six of the 12 infants were on continuous mandatory ventilation (CMV) and six were on synchronised intermittent mandatory ventilation (SIMV). Synchronous breaths were significantly higher on SIMV than on CMV ($p=0.003$). Active expiration was significantly higher on SIMV than on CMV ($p<0.001$). The proportion of breaths with prolongation of expiration was significantly higher on CMV than on SIMV ($p<0.001$). There was no significant difference in the occurrence of augmented inspirations between the two modes (Table 6.1).

	Pattern of interaction (%)			
Mode	Synchronous	Active expiration	Prolonged expiration	Augmented inspiration
CMV n=6	21	32.5	42.7	3.8
SIMV n=6	28.4	64.9	4.1	2.6

Table 6.1 Distribution of interactions across each mode (expressed as percentages of interactions within total breaths analysed)

6.3.2 Comparison of different levels of volume targeting

Fifteen infants with a median gestational age of 38 weeks and a median birthweight of 3.1 kg were studied at a median postnatal age of 5 days. Five of the fifteen infants were on continuous mandatory ventilation (CMV), seven were on synchronised intermittent mandatory ventilation (SIMV) and three were on assist/control ventilation (ACV). In four of the neonates (one neonate on CMV, three on triggered ventilation), during ventilation at the volume-target of 4ml/kg, no ventilator breaths were being delivered. This occurred in cases where the infant's spontaneous effort was so vigorous, that the tidal volume per breath was easily generated by the infant alone, and the ventilator provided only the set PEEP and perhaps a PIP of 1-2 cm of H_2O above it (Figure 6.6). Data from these neonates were excluded from comparison at all levels.

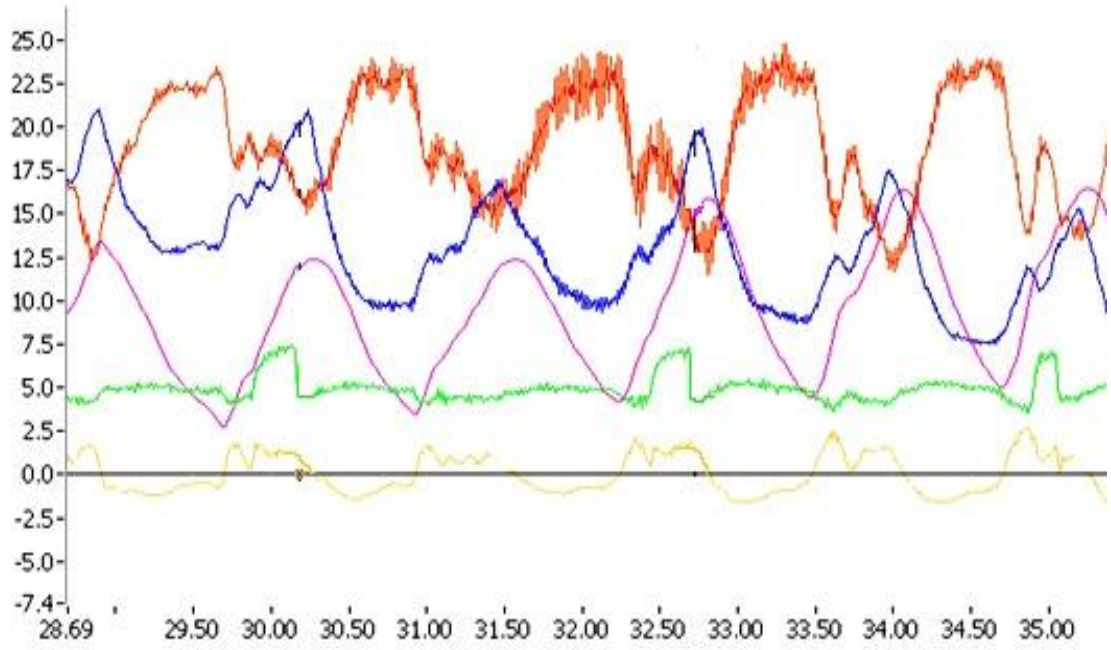


Figure 6.6 Peak inflation pressures of 7 cm of H_2O (PEEP 5) at VT 4ml/kg

Patient-ventilator interactions from four neonates on CMV and seven neonates on SIMV were analysed (Table 6.2). Synchronous interactions were significantly more common at VT of 4ml/kg compared to no VT or VT of 6ml/kg ($p<0.0001$). Synchrony was also more common with no VT compared to 6ml/kg ($p=0.0003$). Active expiration was more common with no VT compared to VT of 6ml/kg ($p=0.02$). Prolonged expiration was more common with no VT ($p=0.03$) and VT of 6ml/kg ($p<0.0001$) compared to VT at 4ml/kg, and also more common at 6ml/kg compared to no VT ($p<0.0001$). Augmented inspirations were uncommon and did not differ significantly between VT levels. Apnoea was significantly less common when infants were ventilated using VT of 4ml/kg compared to no VT or 6ml/kg ($p<0.0001$).

	Pattern of interaction (%)				
	Synchrony	Active expiration	Prolonged expiration	Augmented inspiration	Apnoea
No VT	26	53	13	2	6
VT 4ml/kg	38	51	8	3	0
VT 6ml/kg	16	46	29	2	7

Table 6.2 Percentages of patient-ventilator interactions by VT level (n=11)

Active expiration was significantly more common during mandatory ventilation than triggered ventilation at a VT level of 4ml/kg ($p<0.0001$). Active expiration was significantly more common during triggered ventilation when no VT or VT of 6ml/kg were used ($p<0.0001$ and $p=0.003$ respectively) (Table 6.3).

	Percentage of interactions classified as active expiration (%)		
	Mandatory ventilation n=4	Triggered ventilation n=7	p value
No VT	52	68	<0.0001
VT 4ml/kg	77	37	<0.0001
VT 6ml/kg	39	50	0.003

Table 6.3 Comparison of active expiration during mandatory and triggered ventilation at different levels of volume-targeting

6.4 Discussion

This study has demonstrated that the spontaneous respiratory efforts of mechanically ventilated infants born at or near term show distinct interactions with ventilator inflations. Some patterns of interaction fit with known neonatal respiratory reflexes such as the Hering-Breuer reflexes and Head's paradoxical reflex. This has previously been demonstrated in prematurely born ventilated infants (31), but to my knowledge the first time it has been described in a ventilated term population. Respiratory reflexes have been described in non-ventilated infants born at term (120), and while the reflexes have been shown to become more difficult to stimulate with increasing postnatal age (119, 121) the infants in this study were studied at a median postnatal age of 5 days. Augmented inspirations are known to be more frequent soon after birth, tailing off with postnatal age (100, 122), which fits with the low incidence of augmented inspirations noted in this study. It is highly probable that the patterns of interaction described in this study are produced due to provocation of respiratory reflexes by mechanical inflations.

It is appreciated that a drawback of this study is the small numbers of patients within the groups compared. Only at 4ml/kg was active expiration significantly less on triggered ventilation. An explanation for this phenomenon might be that the suboptimal volume-target caused the infants to make efforts to supplement their minute volume, in response to which the ventilator delivered low inflation pressures over shorter inflation times as the volume target was achieved or exceeded by infant effort. The low inflation pressure, delivered within a period that did not extend into the infant's natural expiratory phase, would be unlikely to provoke an active expiration.

Whether or not a particular kind of patient-ventilator interaction is associated with a particular clinical outcome would be a useful question that this study did not address. Active expiration in prematurely born infants is associated with pneumothoraces (62), but none of the infants in this study developed a pneumothorax. Active expiration did occur on SIMV - this likely reflects that during SIMV inflation may extend into expiration. It would be interesting to assess infant-ventilator interactions on pressure-support ventilation (PSV), as by design, PSV allows the infant to control the onset of the ventilator's expiratory cycle.

In terms of implications for clinical practice, this study demonstrates that use of conventional triggered modes such as SIMV and ACV does not necessarily mean more synchronous patient-ventilator interactions. Spontaneously breathing infants ventilated with triggered modes with VT at the lower end of the physiological range experience lower rates of active expiration, but this may indicate significant effort on the infant's part.

Chapter 7: In vitro study of the effect of proportional assist ventilation on work of breathing

7.1 Introduction

The aim of this study was to determine the effects of increasing elastic and resistive unloading, using pressure-volume curves constructed from tidal volumes and both airway and “pleural” pressure, to help define optimal settings for clinical practice.

7.2 Methods

7.2.1 Protocol

The dynamic lung model, incorporating a ‘pleural space’ and manually retractable ‘diaphragm’, was designed to represent respiratory distress syndrome (RDS). The model is described in detail in the methods chapter. The compliance and resistance of the lung model were 0.4ml/H_2O and 200 cmH_2O/L/sec respectively.

7.2.1.1 Elastic Unloading

The ventilator (Stephanie® neonatal ventilator; F Stephan, Gackenbach, Germany) was then changed to PAV mode with an airway pressure limit of 25 cmH_2O and PEEP of 5 cmH_2O. The airway pressure limit was imposed to avoid ‘runaway pressures’ (progressive increase in inflation pressure with every breath due to positive feedback) that can occur with overcompensation for elastic unloading (85). During PAV, the ‘diaphragm’ was retracted manually at least 10 times to simulate breathing efforts, generating tidal volumes as close as possible to 3 ml (i.e. 6ml/kg for a 500g baby) The tidal volume displayed on the ventilator was used to guide the extent of the retraction of the rubber film.

Baseline assessments were made with elastic unloading and resistive unloading at zero. Measurements were repeated after the elastic unloading was increased in steps of 0.5 cmH_2O/ml until the elastic unloading was equivalent to 2.0 cmH_2O/ml.

Pressure-volume loops were constructed on 5 consecutive inflations at each level of elastic unloading for the ventilator inflations and for the lung model and work of breathing calculated by dividing the aggregate of the tidal volume and inflation pressure by two (123). The result was then divided by the tidal volume to correct from errors due to differences in inflation volumes.

7.2.1.2 Resistive unloading

The procedure described above was repeated but with the elastance unloading maintained at zero, while the resistive unloading was increased by 25 cm H_2O/L/sec increments up to 200 cm H_2O/L/sec.

A computer program (LabChart7, ADInstruments, Dunedin, New Zealand) was used to measure the inspiratory resistive work of breathing i.e. the area of the pressure-volume loop above the inspiratory-expiratory line (124), again on 5 consecutive inflations.

7.2.2 Measurements

Airflow was measured by a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (MP45, range±2 cm H2O; Validyne, Northridge, California, USA). Tidal volume was obtained by digital integration of the flow signal. The pneumotachograph was inserted between the endotracheal tube (ETT) and ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45,

range±100 cm H2O; Validyne). The signals from the pressure transducers were amplified using a carrier amplifier (CD 280; Validyne). P_{pl} was recorded using a differential pressure transducer (MP45, range±100 cm H2O; Validyne). The pressure and flow signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) using Spectra® software v 3.0.0.9 (Grove Medical, Hampton, UK) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50; National Instruments, Austin, Texas, USA).

7.2.3 Statistical analysis

All statistics were carried out using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA).

7.3 Results

The median tidal volume generated by the retraction of the diaphragm was 3.8 ml (range 3.1-4.4ml) during elastic unloading and was 3.4 ml (range 2.4-4.3ml) during resistive unloading.

7.3.1 Elastic unloading

The elastic WOB corrected for tidal volume provided by the ventilator rose from 0.18 (SD 0.09) gm.cm/ml with zero unloading to 3.75 (SD 0.24) g.cm/ml with unloading of 2.0 cm H_2O/ml in a linear manner. The corresponding WOB measurements from the pressure-volume curves of the lung model fell from 7.53 (SD 0.48) to 2.17 (SD 0.39) g.cm/ml (Table 7.1, Figure 7.1). Although these reductions were also linear, the WOB of the lung model fell approximately 30% more than the corresponding increase in the WOB provided by the ventilator. The pressure-volume loops showed considerable

deviation from the patterns expected if the ventilator's rise in inflation pressure exactly matched the tidal volume (Figs 7.3-7.7).

		Level of elastance unloading (cm H_2O/ml)				
		None	**0.5**	**1.0**	**1.5**	**2.0**
Elastic WOB (g.cm/ml)	**Lung model**	7.53	6.57	4.60	3.29	2.17
	Ventilator	0.18	1.12	1.97	3.15	3.75

Table 7.1 Work of breathing for lung model and ventilator with increasing levels of elastic unloading corrected for tidal volume delivered

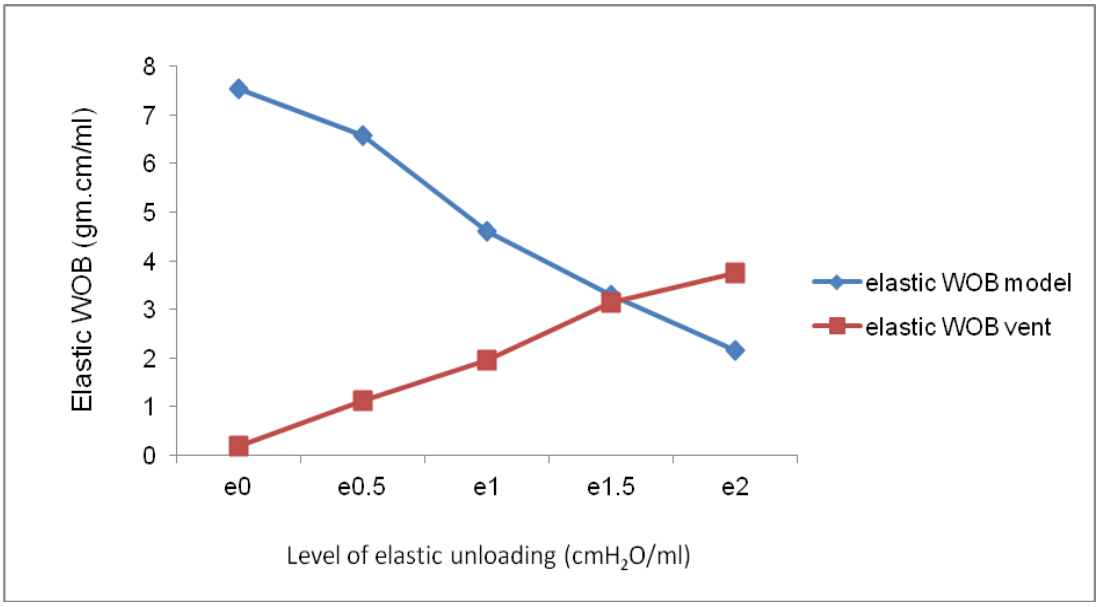


Fig 7.1 Changes in WOB for the lung model and ventilator with increasing levels of elastic unloading

7.3.2 Resistive unloading

The resistive WOB provided by the ventilator rose from 0.28 (SD 0.16) g.cm with zero unloading to 7.17 (SD 1.4) g.cm with resistive unloading of 200 cm H_2O/L/sec. This rise was approximately linear. The resistive unloading of the lung model showed an almost random pattern with a higher WOB of 9.5 (SD 1.85) g.cm at 200 cm H_2O/L/sec compared to 6.82 (SD 1.3) at zero unloading (Table 7.2, Figure 7.2). These results were due to the complex pressure volume loops of the lung model (Figs 7.8-7.16) and the relatively low inflation pressures generated by the ventilator even at maximum unloading (6 cmH_2O).

		Level of resistance unloading (cm H_2O/L/sec)								
		None	**25**	**50**	**75**	**100**	**125**	**150**	**175**	**200**
Resistive WOB (g.cm)	**WOBmodel**	6.82	10.15	12.58	8.53	8.99	7.65	3.37	6.49	9.5
	WOBvent	0.28	0.23	1.64	2.51	4.48	5.27	4.49	5.77	7.17

Table 7.2 Work of breathing for lung model and ventilator with increasing levels of resistive unloading corrected for tidal volume delivered

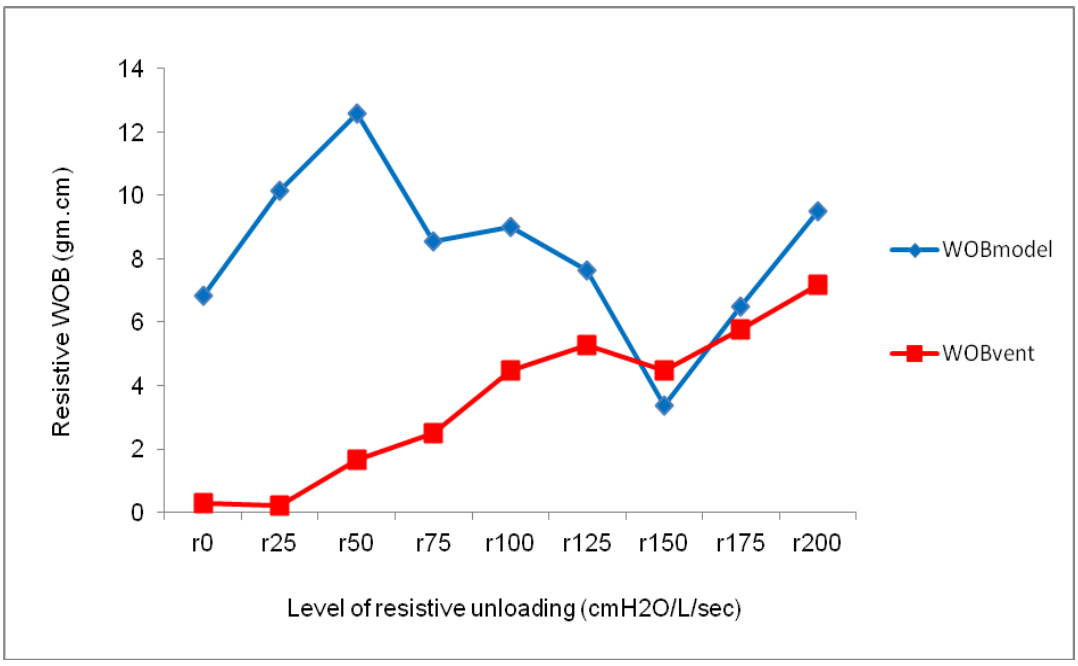


Figure 7.2 Changes in WOB for the lung model and ventilator with increasing levels of resistive unloading

7.4 Discussion

This study demonstrates that although during elastic unloading there are complex pressure-volume loops PAV is very effective in reducing elastic WOB. In contrast, no benefit was demonstrated from resistive unloading. The success of the elastic unloading was surprising in view of the trigger delay and the differences in oesophageal and airway pressure wave forms demonstrated in our previous publication and are responsible for the complex pressure volume loops demonstrated in Figs 7.3-7.7. In the previous publication the fall in oesophageal pressure with increasing elastic unloading closely matched the rises in airway pressure. It is likely that the complexity of the pressure-volume curves of the lung model led to an under calculation of the WOB as elastic unloading is increased. This would explain why the WOB of the lung model falls by approximately 30% more than the increase in WOB provided by the ventilator.

Although the ventilator appeared to perform well, increasing inflation pressures appropriately with increasing levels of resistive unloading, it was not possible to demonstrate any consistent or significant corresponding fall in WOB in the lung model. This may be due to the complex pressure-volume loops in the lung model. Also, although the resistance was high the main WOB component was elastic and more promising results may have been found in a high compliance and high resistance model. It is however difficult to think of any clinical neonatal respiratory problem which would generate this situation. In conclusion, these data provide further evidence that PAV is highly effective in reducing the elastic WOB and has a role in neonatal respiratory support where the main problem is a low compliance.

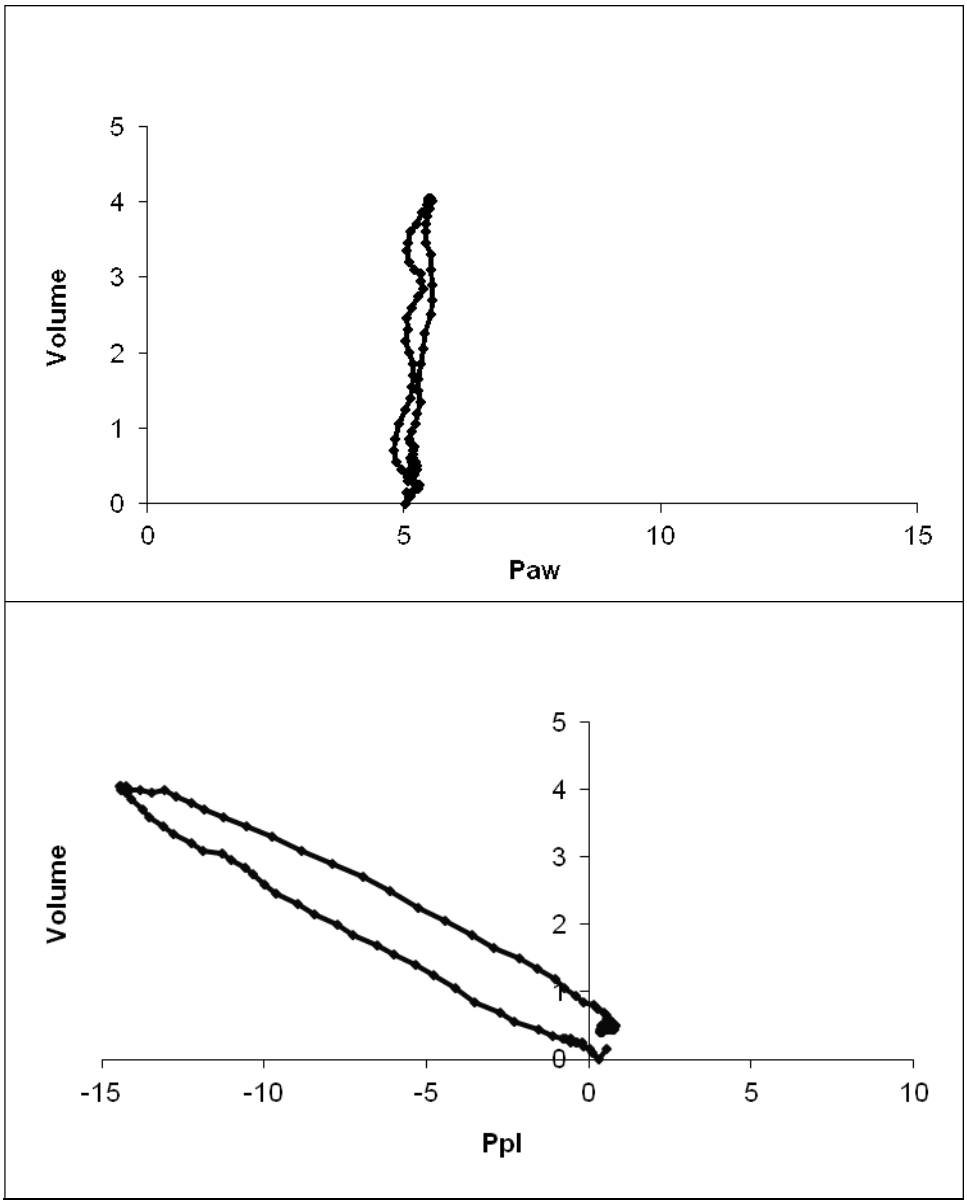


Fig 7.3 Pressure-volume loops for zero elastic unloading

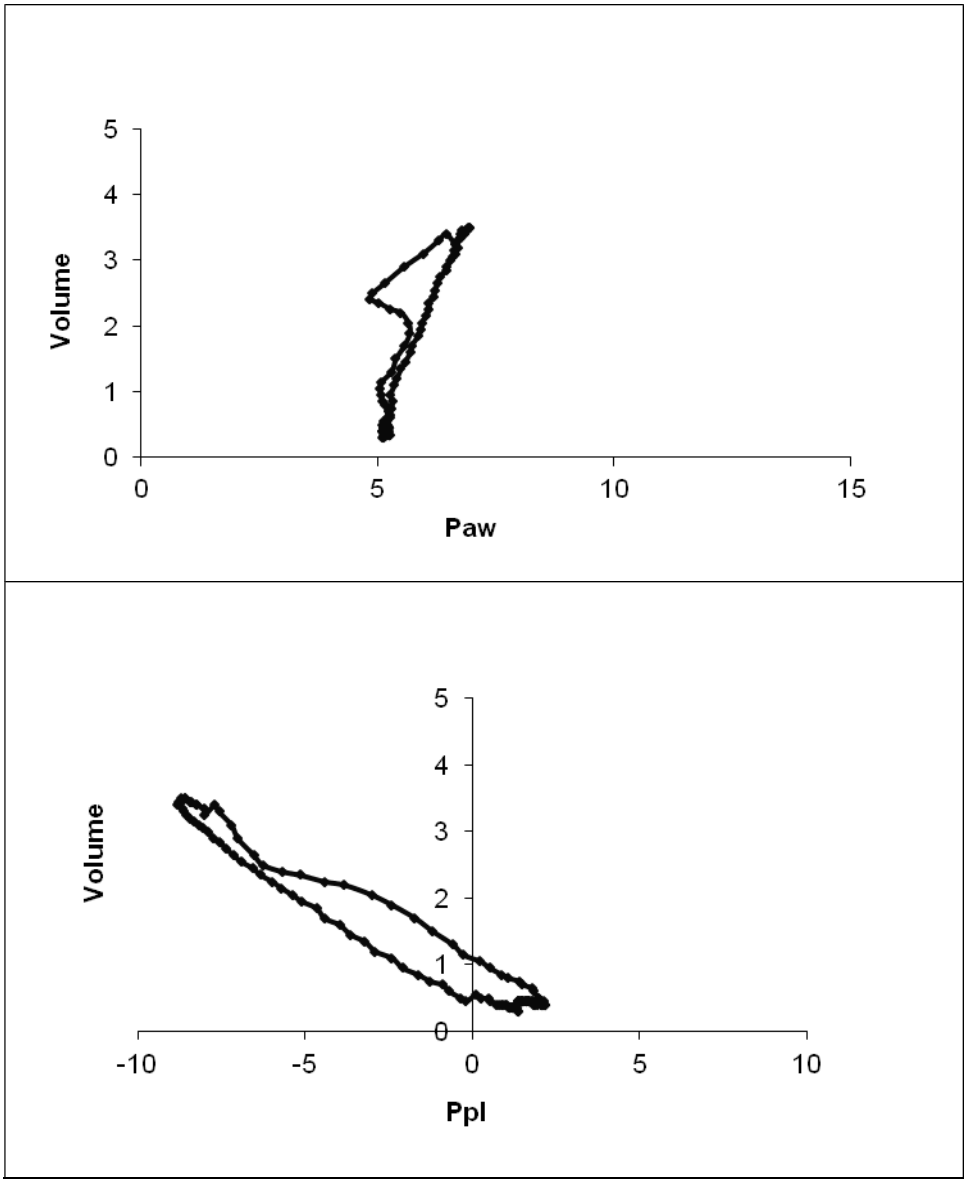


Fig 7.4 Pressure-volume loops for elastic unloading of 0.5 cm.H_2O/ml

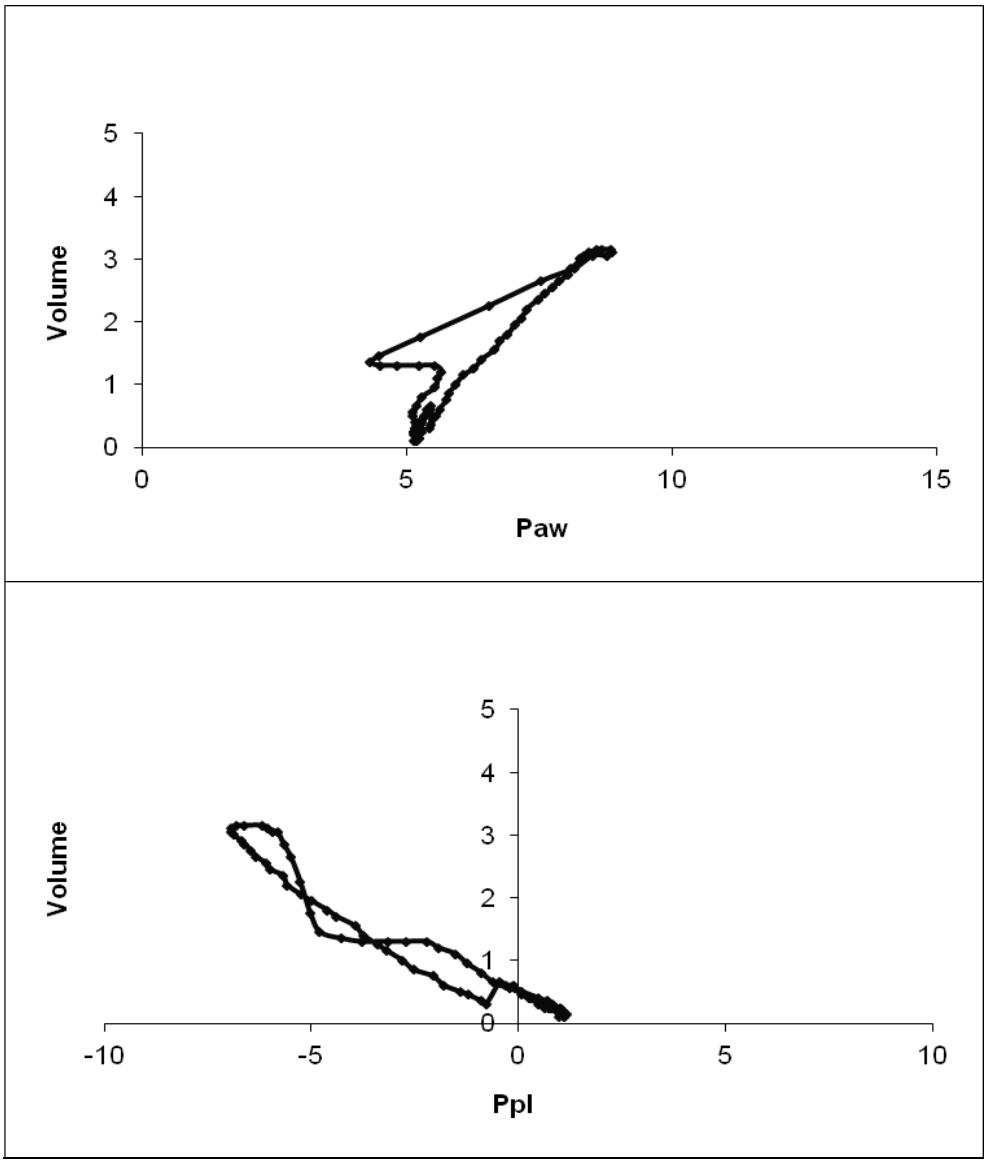


Fig 7.5 Pressure-volume loops for elastic unloading of 1 cm H_2O/ml

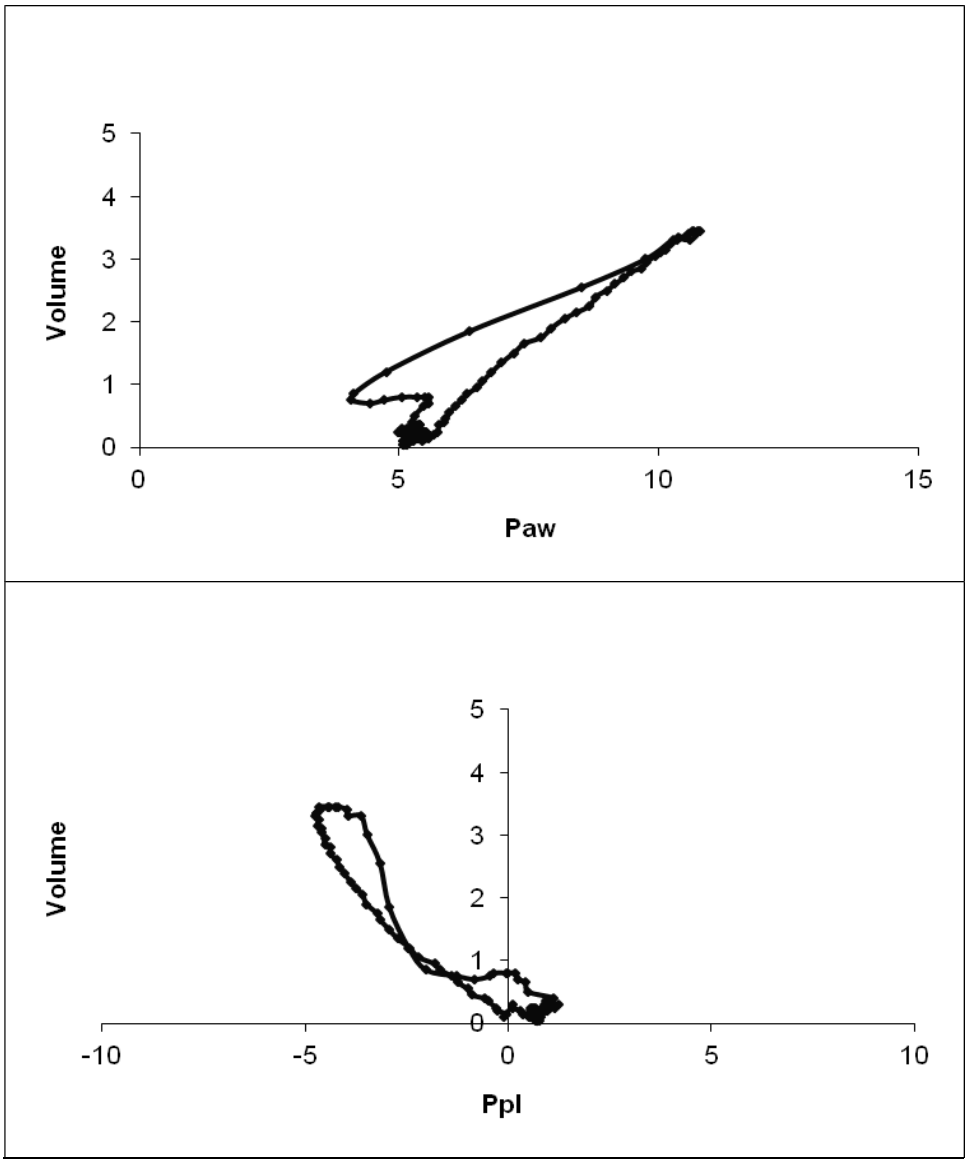


Fig 7.6 Pressure-volume loops for elastic unloading of 1.5 cm H_2O/ml

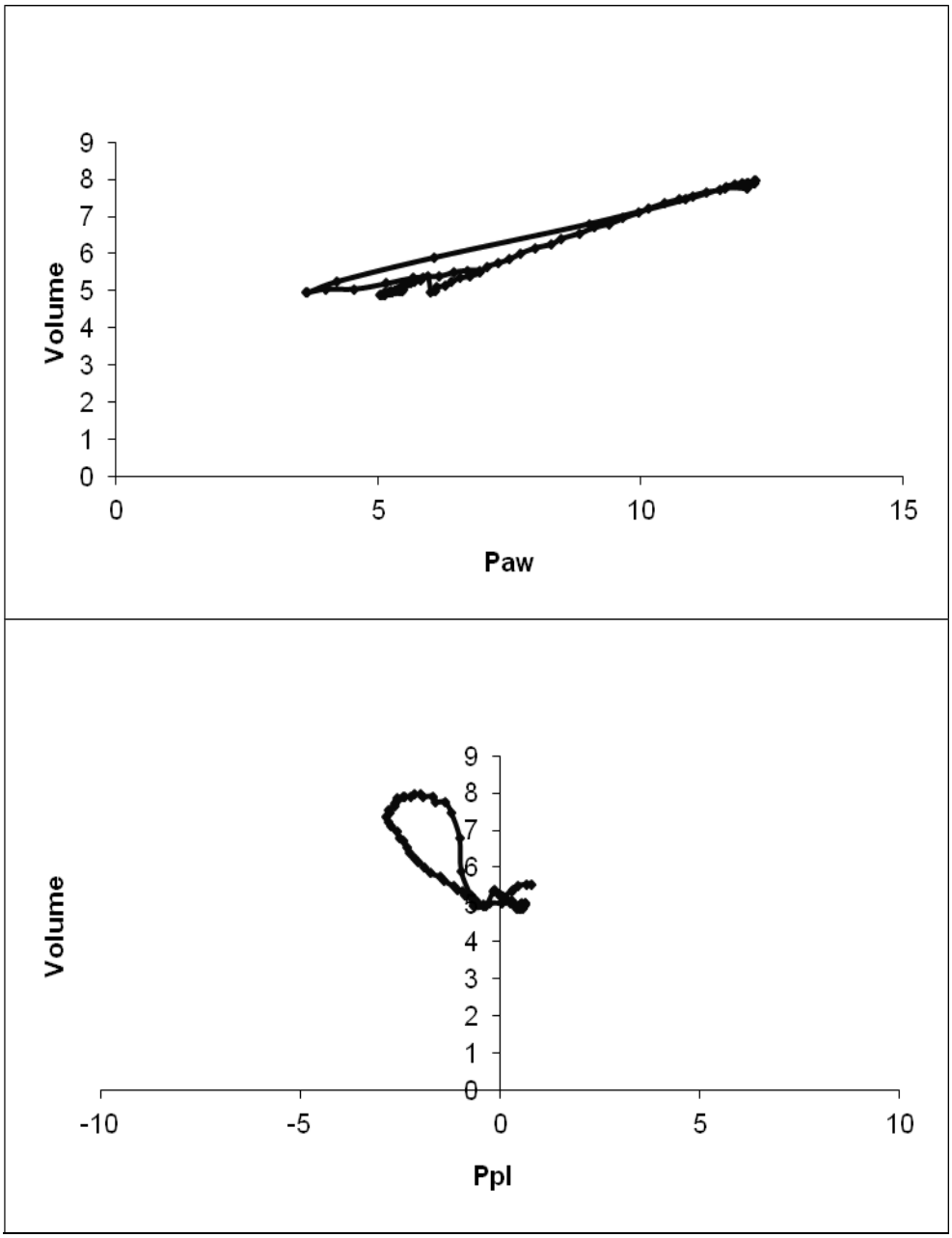


Fig 7.7 Pressure-volume loops for elastic unloading of 2 cm H_2O/ml

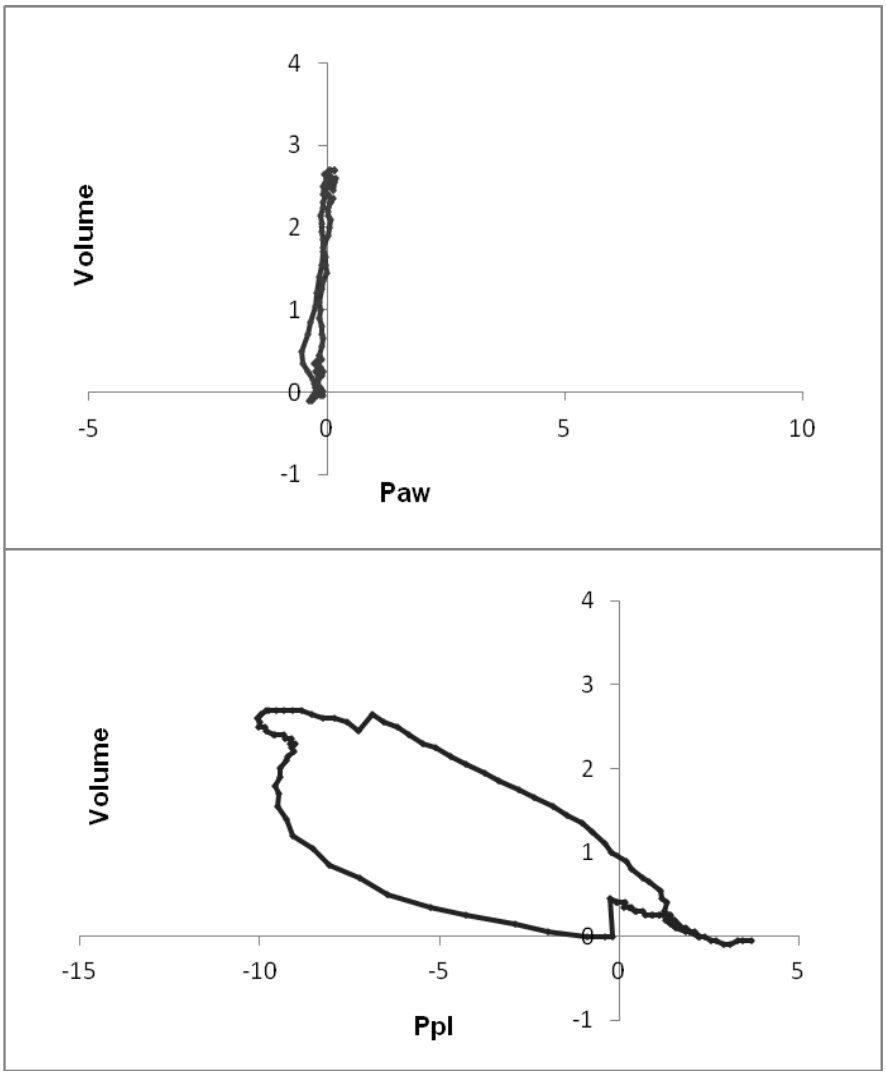


Figure 7.8 Pressure-volume loops for zero resistive unloading

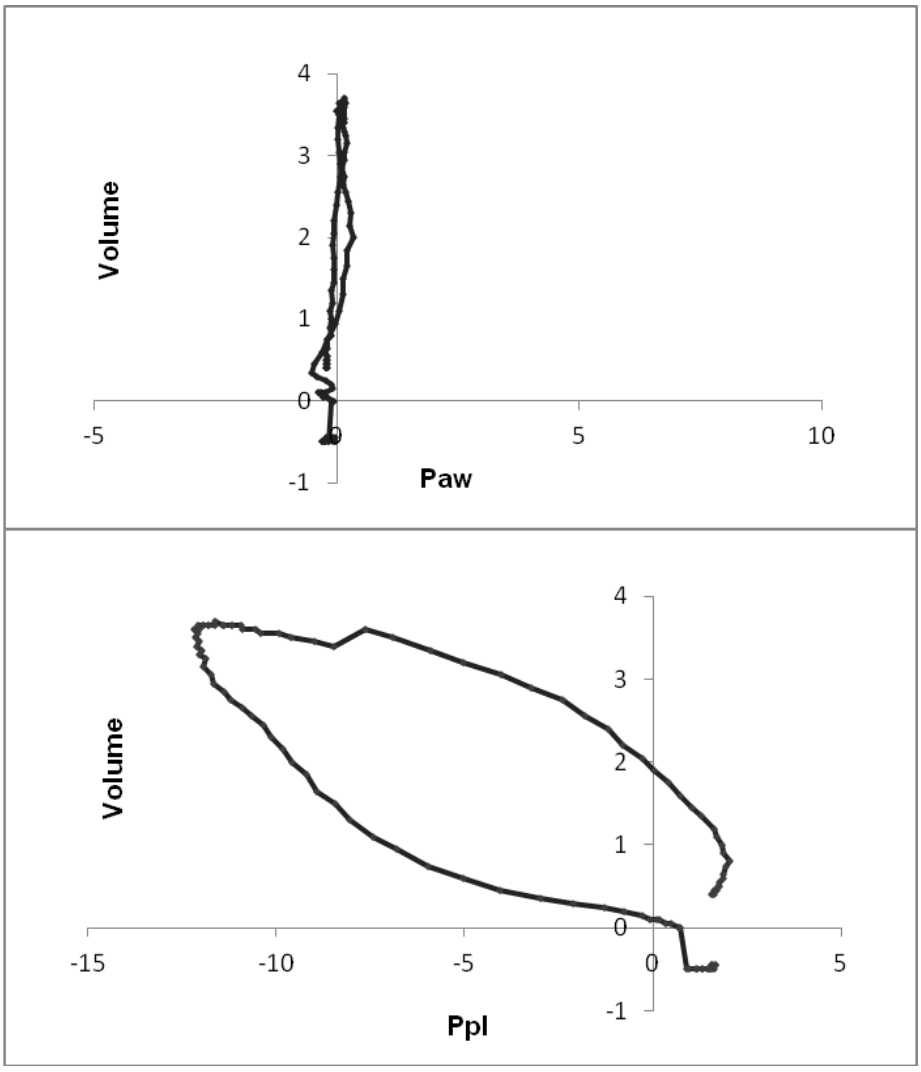


Fig 7.9 Pressure-volume loops for resistive unloading of 25 cm H_2O/L/sec

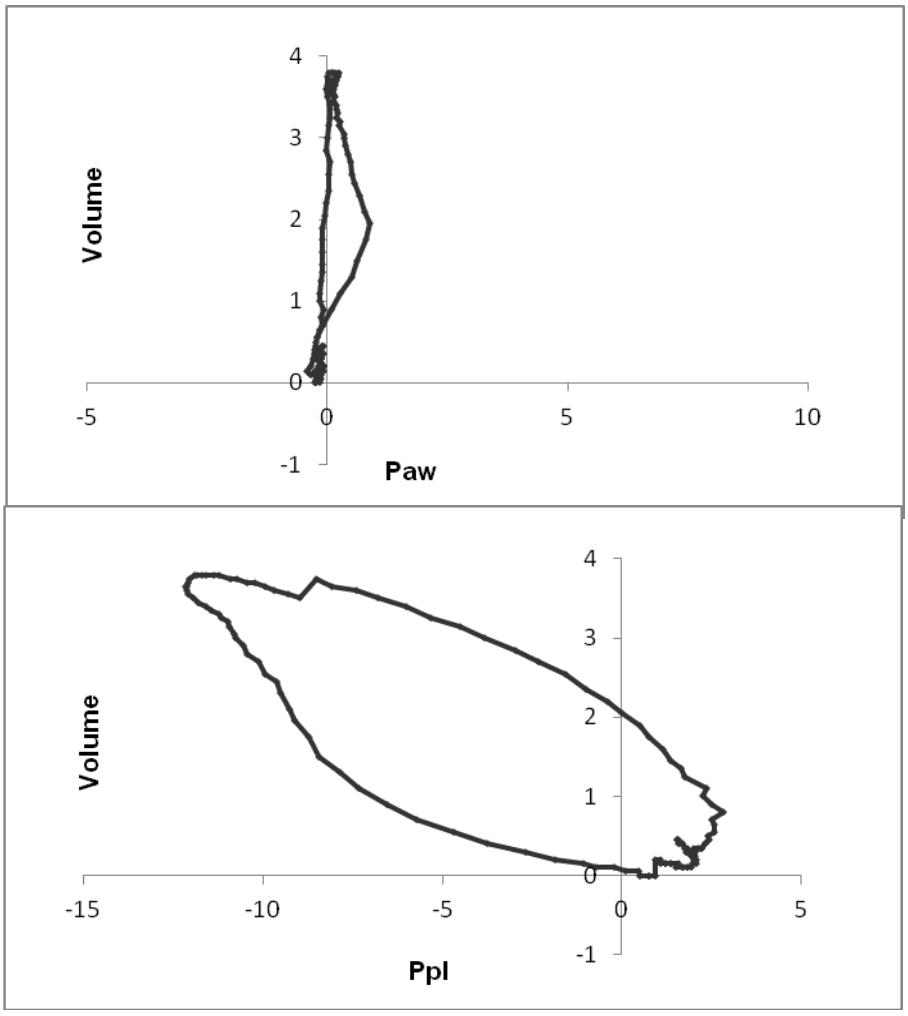


Fig 7.10 Pressure-volume loops for resistive unloading of 50 cm H_2O/L/sec

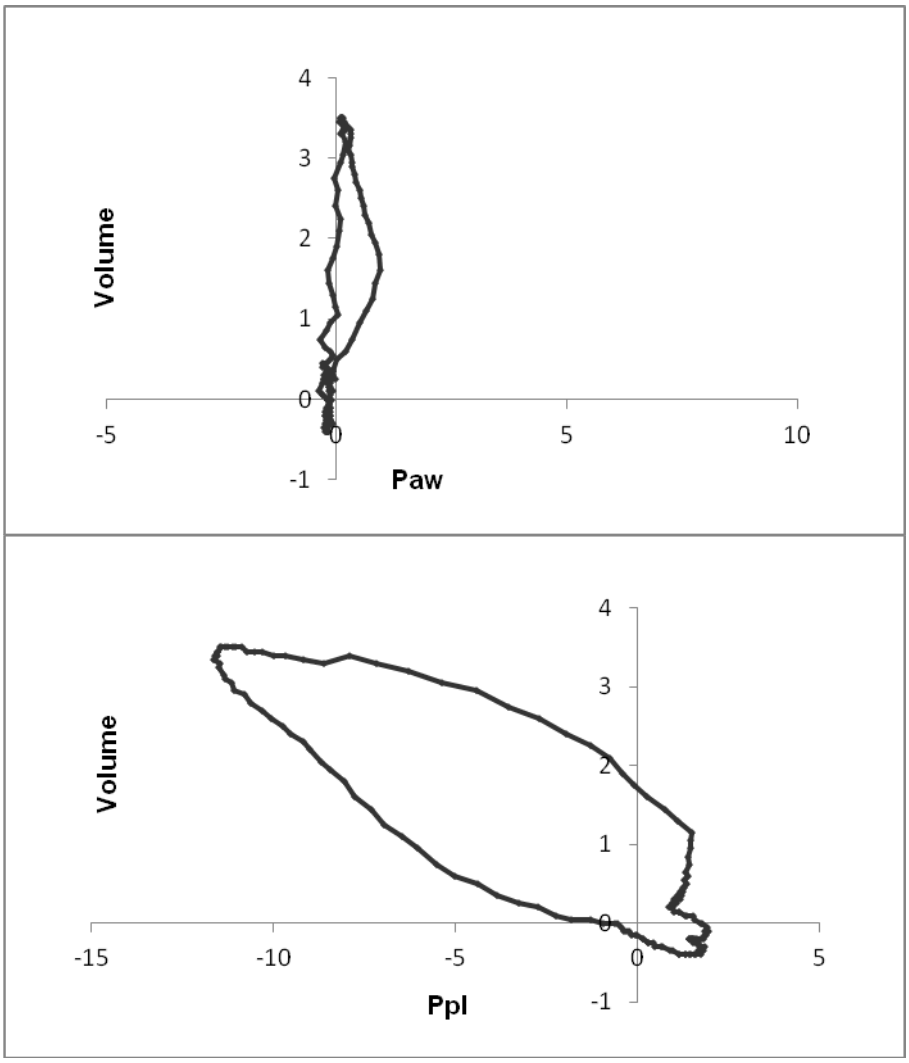


Fig 7.11 Pressure-volume loops for resistive unloading of 75 cm H_2O/L/sec

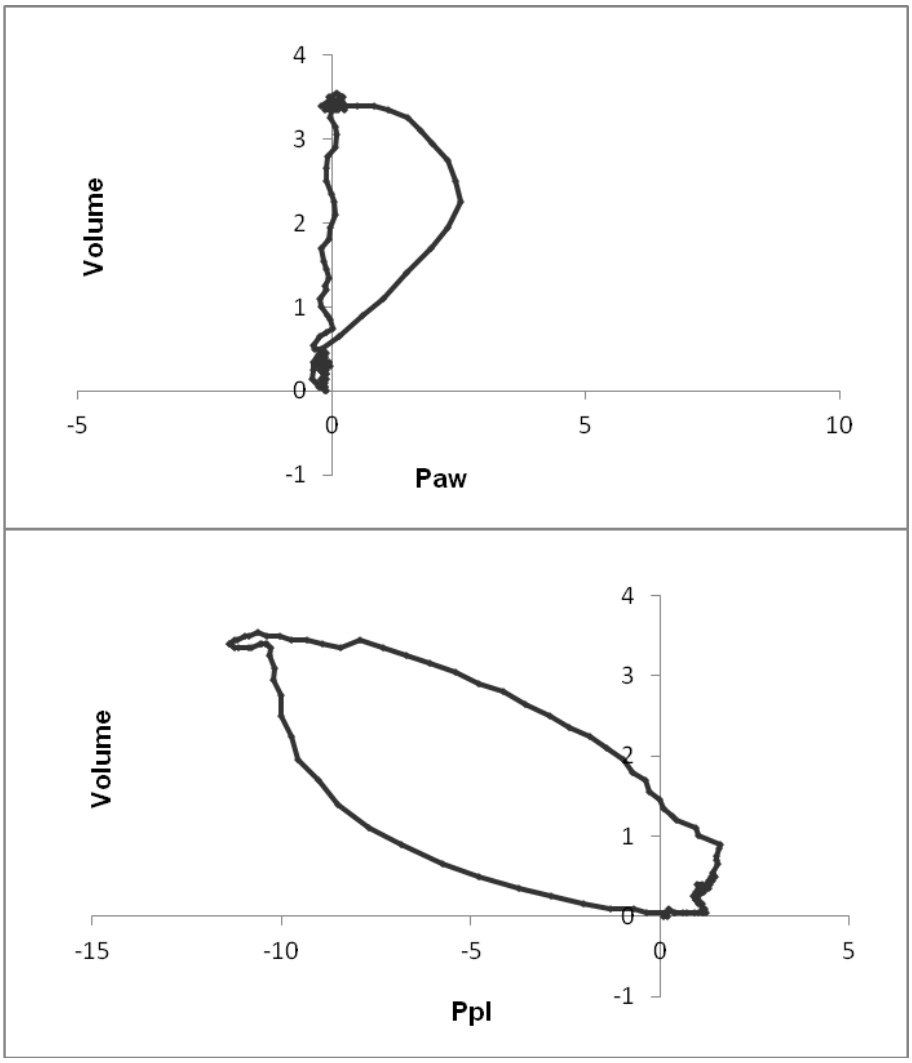


Fig 7.12 Pressure-volume loops for resistive unloading of 100 cm H_2O/L/sec

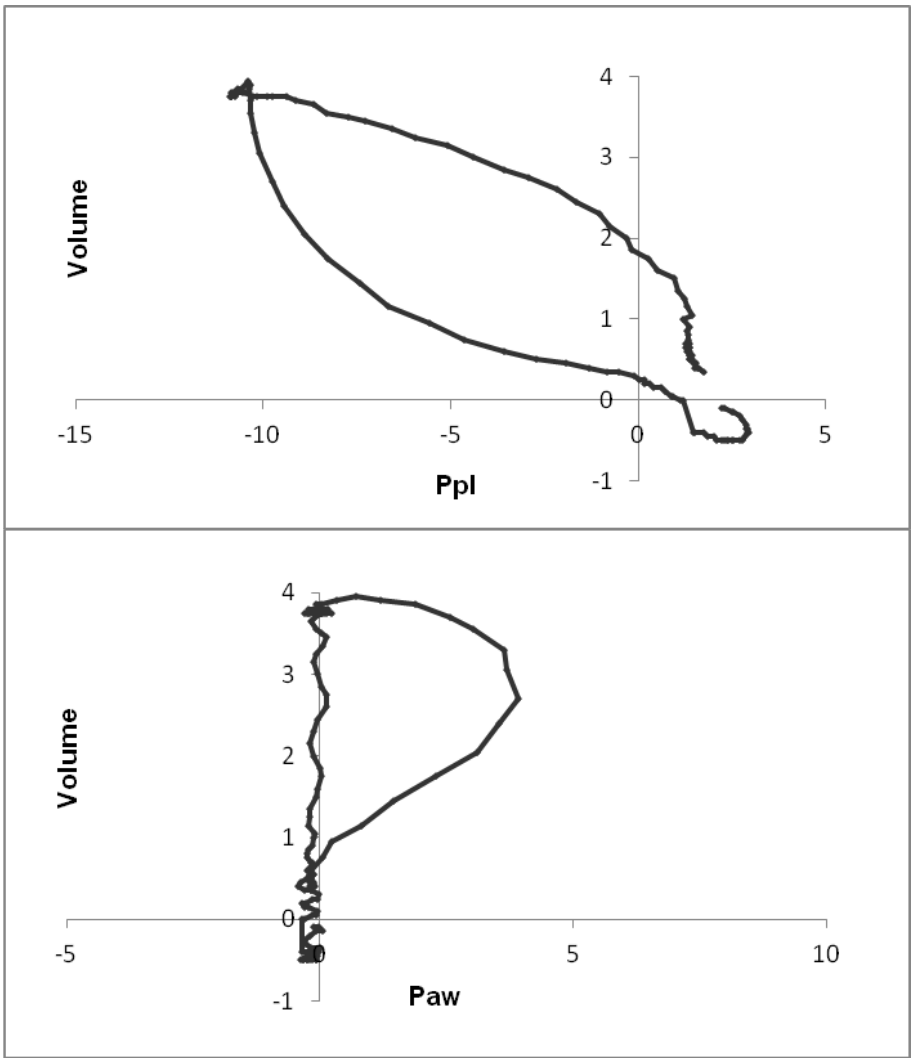


Fig 7.13 Pressure-volume loops for resistive unloading of 125 cm H_2O/L/sec

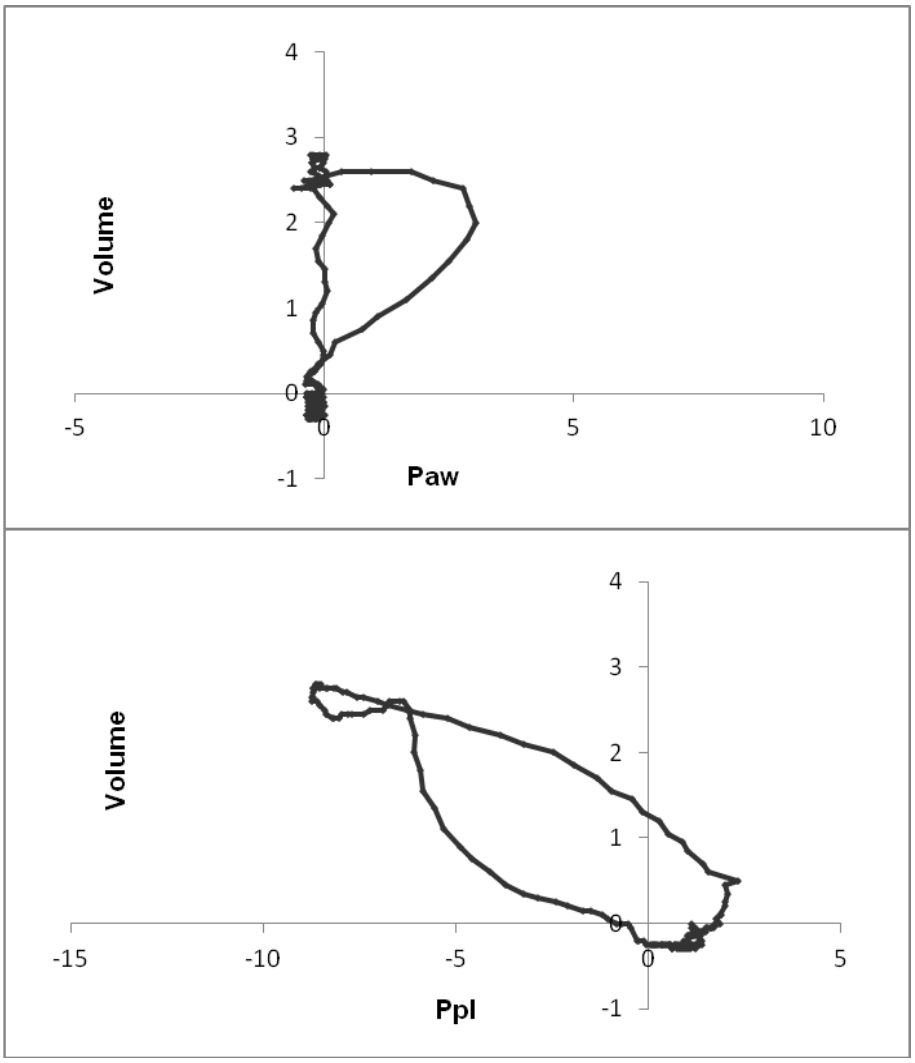


Fig 7.14 Pressure-volume loops for resistive unloading of 150 cm H_2O/L/sec

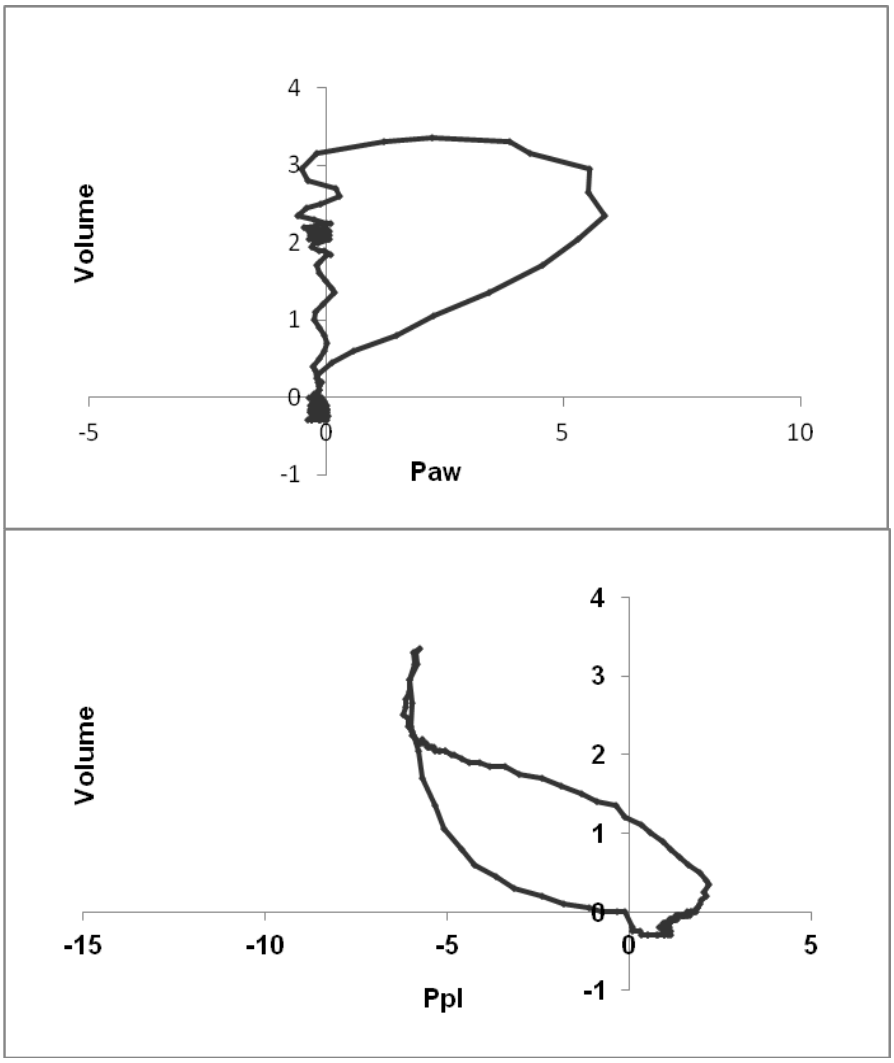


Fig 7.15 Pressure-volume loops for resistive unloading of 175 cm H_2O/L/sec

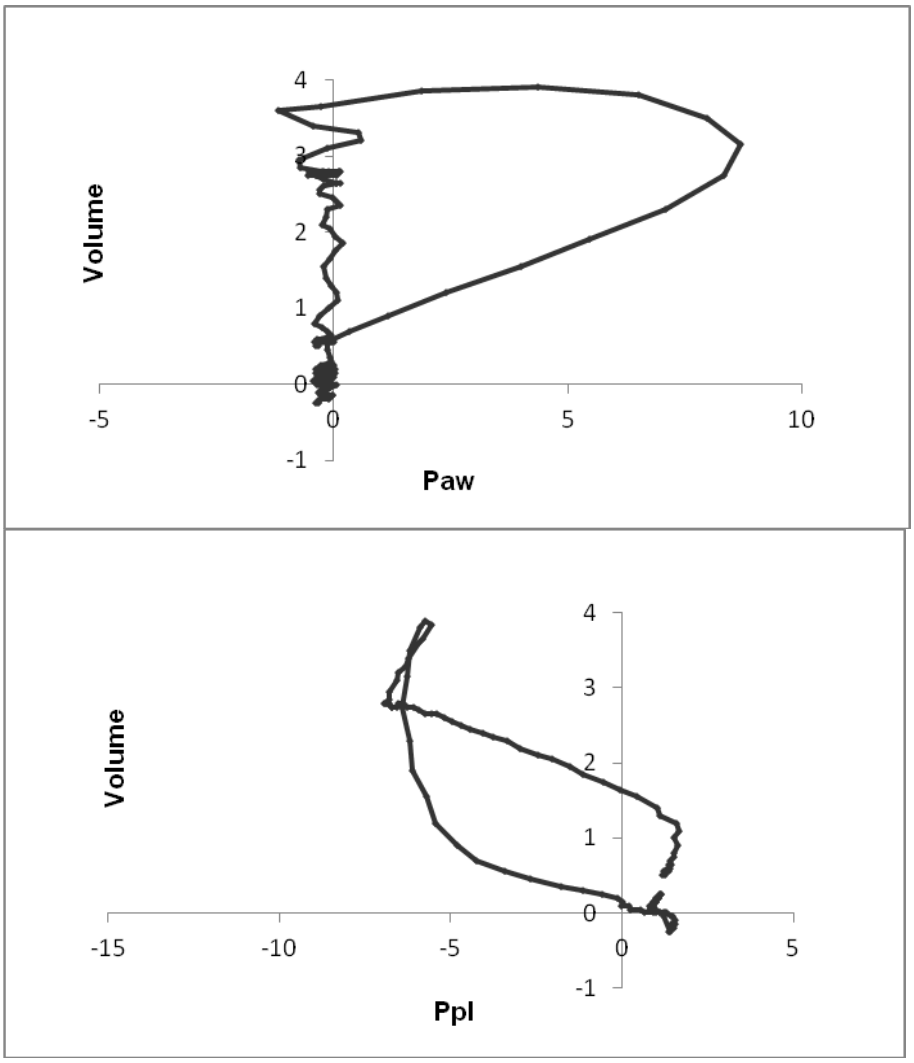


Fig 7.16 Pressure-volume loops for resistive unloading of 200 cm H_2O/L/sec

Chapter 8: Discussion

8.1 Results from this thesis and the current literature

8.1.1 National survey

This survey provides an overarching picture of clinical practice focussed on respiratory support provided to infants born at term by neonatal units across the United Kingdom. There are no other published surveys to date focussing exclusively on the respiratory management of term born infants. Dani's survey (125) focussed on the respiratory management of infants with RDS admitted to Level 3 NICUs in Italy; it does not differentiate between prematurely born and term infants, but the focus on RDS suggests that the data would relate more to management of prematurely born babies as RDS is more common in this group (11). Though the surveys were structured differently, in infants with RDS cared for on NICUs, Dani's study compared to the one reported in this thesis reports less use of CMV (8% versus 14%), SIMV (13% versus 30%) and VTV (18% versus 26%), similar use of ACV (21% versus 19%) and greater use of HFOV (4% versus 0%).

8.1.2 Volume-targeted ventilation

An assessment of WOB at different levels of volume-targeting in term born infants demonstrated that 5ml/kg was an optimal volume target, being associated with significantly less WOB than at 4ml/kg and without the risk of apnoea secondary to hypocarbia noted at 6ml/kg. An RCT comparing VTV to PLV in prematurely born infants did not demonstrate any difference in time to weaning but VTV was associated with significantly less hypocarbia. Neumann (126) demonstrated a negative association of respiratory dead space (defined as the combined anatomical and appliance dead space) and gestational age in a prematurely born cohort, with dead space of the

ventilatory equipment contributing substantially to respiratory dead space. If volume-targets are set at a particular level, then changes in dead space with gestation will impact accordingly on the effective tidal volume. These findings should be taken into consideration when designing future trials assessing VTV.

Peng's recent systematic review and meta-analysis of studies comparing VTV to PLV (127), assessed eighteen studies, one of which was excluded from the Cochrane review (128) and five of which were not included in the Cochrane review (129-133). Of those studies, one (129) is a publication accessible only via China National Knowledge Infrastructure. Swamy's study (130) is an evaluation of further outcomes from data collected as part of an earlier RCT (134). Liu's study (131) is published in Chinese with an abstract available in English – it was an RCT of newborns with severe RDS, comparing SIPPV + volume guarantee (delivered by the Dräger Babylog 8000-plus) with HFOV (delivered by the Sensormedics 3100A) and pressure-limited IMV (Delivered by the VIP Bird). The infants studied ranged in gestation from 27 to 35 weeks, which brings part of the patient population into the 'near-term' category. The RCTs of Duman (132) and Guven (133) both compared VTV (volume guarantee) to PLV in prematurely born infants with RDS using the Dräger Babylog 8000-plus. The new result demonstrated by the Peng meta-analysis is the significant reduction in the incidence of BPD (defined as oxygen dependency at 36 weeks postmenstrual age). In the randomised study comparing VTV to PLV described in Chapter 5, there were significantly fewer episodes of hypocarbia in the first 72 hours in the VTV arm. This is in keeping with results from both meta-analyses (34, 127).

Outcome	Wheeler, 2010	Peng, 2014
Death	RR 0.80 [95% CI 0.53, 1.20]	RR 0.73 [95% CI 0.51, 1.05]
Incidence of BPD (36 weeks)	RR 0.73 [95% CI 0.53, 1.00]	RR 0.61 [95% CI 0.46, 0.82]
Mechanical ventilation (days)	MD -2.36 [95% CI -3.90, -0.83]	MD −2.0 [95% CI -3.14 to -0.86]
Grade 3/4 IVH	RR 0.71 [95% CI 0.45, 1.11]	RR 0.55 [95% CI 0.39, 0.79]
PVL	RR 0.41 [95% CI 0.15, 1.16]	RR 0.33 [95% CI 0.15, 0.72]
Pneumothorax	RR 0.46 [95% CI 0.25, 0.84]	RR 0.46 [95% CI 0.25, 0.86]
Hypocarbia (episodes)	RR 0.56 [95% CI 0.33, 0.96]	RR 0.56 [95% CI 0.33, 0.96]

Table 8.1 Comparison of the results of the two systematic reviews (34, 127)

RR - Risk Ratio

CI - Confidence Interval

MD - Mean Difference

8.1.3 Patient-ventilator interactions

Chapter 6 describes interactions of term born infants with mechanical breaths in patterns which may be explained by respiratory reflexes. Newer modes of ventilation such as pressure support, proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) may offer greater opportunities for patient-ventilator synchrony. NAVA uses an array of electrodes mounted on a nasogastric tube to generate a diaphragmatic electromyography signal also known as electrical activity of the diaphragm (Edi). The Edi signal is transmitted to the ventilator via electronics embedded in the nasogastric tube. The ventilator responds by providing an inflation pressure is directly and linearly in proportion to the Edi. All aspects of the

mechanical breath delivered correspond to the Edi, thus providing, in theory, a breath perfectly tailored to the patient's demand. A crossover study (135) infants and children ventilated on PICU showed that compared to PSV, NAVA was associated with a significantly lower asynchrony index.

8.1.4 Proportional Assist Ventilation

In the *in vitro* study described in Chapter 7, a lung model mimicking RDS was used to assess the efficacy of stepwise increases in elastance and resistance unloading. Elastance unloading was more effective than resistive unloading and in infants with low compliance and high resistance, unloading elastance may be a preferential strategy when using PAV. Unloading resistance should be approached with caution, as, in addition to the lack of efficacy in reducing WOB demonstrated in this study, a previous *in vitro* study (90) demonstrated oscillations in the airway pressure waveform when unloading high levels of resistance (more than 100 cm H_2O/L/s).

Bhat's recent clinical crossover study (136) has demonstrated that in preterm infants, PAV with unloading of elastance by 100% was associated with significantly lower oxygenation index, WOB and increased respiratory muscle strength compared to ACV.

8.2 Strengths and weaknesses of studies

8.2.1 Survey

A good response rate was achieved, overall of 82% of all the neonatal units in the UK, including 90% of the Neonatal Intensive Care Units (NICUs) and 96% of the Local Neonatal Units (LNUs), but only 56% of the Special Care Units (SCUs). The majority of responding SCUs indicated they ventilated less

than ten term newborns per year. Our survey was comprehensive yet concise enough to encourage a complete response. As a result, we were able to obtain an overview from a wide cross-section of UK neonatal units on their approach to respiratory support in term newborns, considering a variety of pathologies and modes of support.

Most surveys of this nature have focussed on units providing a higher level of intensive care (125, 137). We chose to approach all levels of neonatal unit because the need for mechanical ventilation of a term infant may arise in any care setting.

Volume-targeted ventilation is being used in term-born infants with a variety of pathologies, despite the lack of an evidence-base to support this practice. It appears that the evidence-base that exists for prematurely born infants is being extrapolated to the term infant population. It is imperative that studies focussing on optimisation of VTV in term-born infants are carried out, and the study in this thesis addressed that need.

8.2.2 Volume-targeted ventilation

We chose to use volume-target levels of 4, 5 and 6 ml/kg, as term infants have a similar range of physiological tidal volumes to preterm infants (138, 139). We established that 5ml/kg was an optimal tidal volume to target in term infants with respect to work of breathing. Caution should be exercised when using 6ml/kg as it may cause hypocarbia which is known to be associated with adverse outcomes in term infants (38, 39).

In the majority of randomised studies to date, Dräger's volume guarantee has been assessed as the VTV intervention (54, 131-133, 140-144). In this thesis, the TTV^{plus} mode delivered by the SLE 5000 ventilator has been

studied as part of an RCT. The SLE 5000 ventilator is widely used in the United Kingdom (145), therefore this study is relevant to clinical practice.

8.2.3 Patient-ventilator interactions

The term ‘patient-ventilator interaction’ has broad usage, and has been used to reflect work of breathing (146) and variance in tidal volume delivery (147). The study in Chapter 6 may be the first description of patient-ventilator interactions in ventilated term-born infants, reflecting the possible role of respiratory reflexes. Patient-ventilator interactions have been the focus of previous studies assessing new modes of ventilation, such as the comparison of flow-triggered and pressure-triggered SIMV (146) and testing the prototype for the first volume guarantee algorithm (147). The study in Chapter 6 was not designed to take into account association of particular patterns of interactions with clinical outcomes; this is a drawback. The comparisons were not made according to power calculations, which is a limitation due to the opportunistic nature of this study. Data from this study could be used as pilot data to inform power calculations for future studies of newer modes of ventilation aiming to reduce asynchronous interactions or promote synchrony.

8.2.4 *In vitro* study of PAV

The ventilator display was used to determine compliance and resistance of the lung model. A study by Abbasi (148) assessing accuracy of tidal volume, compliance and resistance values as displayed by five different ventilators showed that there was considerable variation in the computation of these variables. The Stephanie, which was the ventilator used in our study, was not assessed in Abbasi’s study. PAV delivered with the Stephanie would, by

design, require utilisation of the values of compliance and resistance provided by the ventilator display. Our study did not include a verification of the Stephanie ventilator's accuracy in measuring these parameters. Verifying the compliance and resistance of the lung model independently and using those values to guide the degree of elastic and resistive unloading would not have been pragmatic, as in clinical practice it would not be feasible to carry out the measurement of the compliance and resistance separately and use those values instead of the ones on the ventilator display.

8.3 Future research

Despite a systematic review demonstrating significant benefits of VTV compared to PLV (34), questions persist about the optimal use of this mode in infants, as the majority of RCTs to date have focussed on preterm infants with RDS. It is important that results from these studies are not extrapolated to term infants or infants with severe BPD. This would necessitate designing large, multicentre studies, adequately powered to enable analysis of subgroups such as term-born infants or infants with specific pathologies such as meconium aspiration syndrome or severe BPD.

The time is right for an RCT to compare PAV to VTV and such a study is in the process of being undertaken by this research group. PAV offers opportunities for superior synchronisation. Whether or not resistance unloading has a place in clinical practice is yet to be determined conclusively; future studies should address this issue.

The potential of Neurally Adjusted Ventilatory Assist (NAVA) may surpass that of PAV. Small crossover (149) and pilot studies (150) have already been

carried out studying the effects of NAVA in infants. The scene has been set for RCTs assessing NAVA, but further studies may be required to clarify the optimal weaning strategy.

Electrical Impedance Tomography (EIT) is a non-invasive method of measuring relative distribution of volume within the lungs and the feasibility of using it in ventilated preterm infants has been demonstrated (151). It has been shown to be a highly reproducible measurement in animal and human studies (152, 153). Along with measures of WOB, respiratory muscle strength and asynchrony, EIT could provide additional information on the efficacy of ventilation techniques. EIT could be used to determine settings for a particular mode in a particular clinical situation (for example, bronchopulmonary dysplasia in preterm infants or meconium aspiration syndrome in term infants), to optimise distribution of volume within the lungs. It would be interesting to study whether better distribution of lung volumes assessed by EIT correlated with better oxygenation and CO_2 clearance, better respiratory muscle strength and reduced work of breathing. If so, EIT could be used as a proxy non-invasive technique within the setting of RCTs comparing different modes of ventilation; its main advantage is that information could be captured continuously, in contrast to the intermittent invasive recordings performed as part of traditional physiological measurements.

Avoidance of invasive modes of ventilation is gaining momentum (154-156) in preterm infants. There is a lack of evidence relating to the use of non-invasive modes in infants born at term and future studies should explore the use of CPAP and biphasic CPAP in this group of patients. Despite these

modalities being used on an increasingly regular basis in paediatric practice, there is a reluctance to use them in term born infants because of a belief, which seems more based in anecdote as opposed to evidence, that term infants will ‘fight’ CPAP and be at a higher risk of air leaks. The reasoning behind this school of thought may be related to term born infants’ greater respiratory drive and ability to generate higher transpulmonary pressures which increase the risk of air leak. Studies of non-invasive modes in term born infants may conclusively establish the safety of CPAP in this population. High-flow nasal cannula therapy is starting to be used in term born infants admitted to NICU with mild-moderate respiratory distress. There is no evidence to support this practice, so studies in this area should be planned in the near future.

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Appendices

A1. Electronic survey

Survey of respiratory support in neonates born at term

1. Demographics

Designation

Hospital / Unit Name

2. Level of intensive care provided (BAPM Standards, 2010)

- ◯ Level 1 (SCBU)
- ◯ Level 2 (Local Neonatal Unit)
- ◯ Level 3 (NICU)

Comment

Neonatal Unit information

3. How many neonates born at term were mechanically ventilated on your unit last year?

- ◯ <10
- ◯ 10-50
- ◯ >50

Comment

4. Which ventilators do you use on your unit for conventional ventilation of neonates born at term? (Please tick all that apply)

- ☐ Dräger Babylog 8000/8000+
- ☐ Dräger Babylog VN500 (new Babylog)
- ☐ SLE 5000
- ☐ Other (please specify)
- ☐ SLE 2000
- ☐ Stephanie
- ☐ VIP Bird Gold

5. Which ventilators do you use on your unit for high-frequency oscillatory ventilation (HFOV) of neonates born at term? (Please tick all that apply)

- ☐ Sensormedics 3100A
- ☐ Stephanie
- ☐ Dräger Babylog 8000+
- ☐ Other (please specify)
- ☐ Dräger Babylog VN500 (new Babylog)
- ☐ SLE 5000

Ventilation modes

6. Please indicate
(a) the primary mode of ventilation on your unit for the following conditions in neonates born at term
(b) if you use volume targeting in conjunction with that mode for each condition (by ticking the box on the far right)

	CPAP	CMV/IMV/IPPV	SIMV	ACV/PTV/SIPPV	Pressure Support	HFOV	+ Volume Targeting
Meconium aspiration syndrome (MAS)	☐	☐	☐	☐	☐	☐	☐
Respiratory distress syndrome (RDS)	☐	☐	☐	☐	☐	☐	☐
Persistent pulmonary hypertension of the newborn (PPHN)	☐	☐	☐	☐	☐	☐	☐
Congenital pneumonia/aspiration	☐	☐	☐	☐	☐	☐	☐
Respiratory support for non-respiratory illness eg, HIE	☐	☐	☐	☐	☐	☐	☐
Congenital diaphragmatic hernia (CDH)	☐	☐	☐	☐	☐	☐	☐
Undergoing gastrointestinal (GI) surgery	☐	☐	☐	☐	☐	☐	☐

Comment

7. If the infant deteriorates on the primary mode of ventilation, which mode(s) would you use as rescue?

	IMV/CMV/IPPV	SIMV	ACV/PTV/SIPPV	HFOV
MAS	☐	☐	☐	☐
RDS	☐	☐	☐	☐
PPHN	☐	☐	☐	☐
Congenital pneumonia/aspiration	☐	☐	☐	☐
Respiratory support for non-respiratory illness eg, HIE	☐	☐	☐	☐
CDH	☐	☐	☐	☐
Undergoing GI surgery	☐	☐	☐	☐

Comment

Ventilator settings

8. Does your unit routinely use volume-targeted ventilation (VTV) in neonates born at term (excluding for research purposes)?

- ◯ Yes (please answer all questions in this section)
- ◯ No (please go to question 12)

9. If your unit uses volume-targeted ventilation in neonates born at term, please indicate your range of tidal volume targeting (ml/kg) for the following conditions

MAS	
RDS	
PPHN	
Congenital pneumonia/aspiration	
Respiratory support for non-respiratory illness eg, HIE	
CDH	
Undergoing GI surgery	

10. If your unit uses volume-targeted ventilation in the following conditions in neonates born at term, please indicate the maximum PIP (cm H2O) you would be prepared to use to achieve the tidal volume target.

MAS	
RDS	
PPHN	
Congenital pneumonia/aspiration	
Respiratory support for non-respiratory illness eg, HIE	
CDH	
Undergoing GI Surgery	

11. When weaning volume-targeted ventilation, what is the minimum target volume you would wean to prior to extubation in a neonate born at term? (ml/kg)

12. Does your unit routinely change a neonate born at term who is on HFOV to conventional ventilation prior to extubation?

- ◯ Yes
- ◯ No

Comment

Adjunct therapies

13. If nitric oxide (NO) is used as an adjunct therapy in a ventilated neonate born at term

What is your starting dose? (ppm)

What is your maximum dose? (ppm)

14. Do you routinely use surfactant therapy for any of the following conditions in neonates born at term? (Please tick all that apply)

- [ ] MAS
- [ ] RDS
- [ ] PPHN
- [ ] Congenital pneumonia/aspiration
- [ ] Pulmonary haemorrhage
- [ ] CDH

Comment

A2. Publications arising from this thesis

Eur J Pediatr (2012) 171:1633–1638
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ORIGINAL ARTICLE

Respiratory support practices in infants born at term in the United Kingdom

Olie Chowdhury · Catherine J. Wedderburn · Silke Lee · Simon Hannam · Anne Greenough

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Abstract Infants born at term requiring mechanical ventilation suffer significant mortality and morbidity, yet few studies have tried to identify the optimum respiratory support for such infants. We, therefore, hypothesised that practice would vary, particularly between different levels of neonatal care provision. The lead clinicians of all 212 UK neonatal units were asked to complete an electronic web-based survey regarding respiratory support practices for term-born infants. Survey questions included the level of neonatal care provided, number of term-born infants ventilated per annum, initial and rescue ventilation modes and whether surfactant or inhaled nitric oxide (NO) were used. The overall response rate was 82 %. A greater proportion of neonatal intensive care units (NICUs) compared to local neonatal units (LNUs) stated that they used volume-targeting, particularly for infants with RDS (p=0.0006) or congenital pneumonia (p=0.0005). High-frequency oscillatory ventilation was stated as initial mode by a greater proportion of NICUs compared to LNUs and special care units (SCUs), particularly for respiratory distress syndrome (p<0.0001) or persistent pulmonary hypertension of the newborn (p<0.001). Continuous mandatory ventilation was stated to be the rescue mode by a greater proportion of LNUs/SCUs compared to NICUs (p<0.0001). Surfactant was stated to be most commonly given for respiratory distress syndrome (79 % of units) and MAS (61 % of units); surfactant use was lowest in SCUs (p<0.0001); inhaled NO was infrequently used by LNUs and SCUs. *Conclusions* There was considerable variation in respiratory support practices for term-born infants, particularly between different levels of neonatal care provision.

Keywords Mechanical ventilation · Infants · Surfactant · Nitric oxide

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Introduction

It has been estimated that 3.6 per 1,000 infants born at term (37–41 weeks of gestational age) require mechanical ventilation [8]. Such infants have a high mortality rate ranging from 9.1 % to 12.2 % [2, 13, 18]. Congenital anomalies are a contributing factor [2, 13], but in one study [18], a mortality rate of 9.6 % to 12.2 % was reported in term-born infants without major congenital anomalies. Ventilated, term-born infants can also suffer considerable morbidity. In one study [8], 5 % of the infants developed chronic lung disease, 7 % developed neurological complications and 24 % developed pneumothoraces. There have, however, been few studies attempting to identify the optimum mode of respiratory support in term-born infants. In the UK, there are three levels of neonatal care provided [3]: Special care units (SCU) provide special care for their own local population, local neonatal units (LNU) provide special and high dependency care and a restricted volume of intensive care (as agreed locally), and neonatal intensive care units (NICU) are larger intensive care units that provide the whole range of medical (and sometimes surgical) neonatal care. SCUs and LNUs should transfer infants with ongoing complex respiratory support requirements to NICUs. Hence, it

seemed likely that practice would vary, particularly between different levels of neonatal care. In addition, given the lack of evidence, we hypothesised that respiratory support practices used for term-born infants might reflect evidence from studies of prematurely born infants. The aim of this study was to test those hypotheses by carrying out a survey of neonatal units in the UK to document current respiratory support practices in term-born infants.

Materials and methods

Lead clinicians of all 212 neonatal units in the UK were identified from the BLISS directory and contact details confirmed by contacting each hospital. Clinicians were sent an email inviting them to complete an electronic web-based survey (Appendix A) from May to July 2011. The survey included questions on the level of neonatal care provided by the hospital, the number of term newborns ventilated per annum and the type of ventilator used. Practitioners were also asked which ventilation mode was used initially and as rescue mode for various conditions and if they extubated infants directly from high-frequency oscillatory ventilation (HFOV). A question regarding continuous positive airways pressure (CPAP) was included in the survey, as we were interested to determine how many units used CPAP initially rather than ventilation modes and for which diagnoses. They were also asked what level of volume-targeting was used and whether surfactant and inhaled nitric oxide (iNO) were administered.

Analysis

Differences in the responses between practitioners from different levels of neonatal care were assessed for statistical significance using the chi-square test.

Results

The response rate was 82 %. Practitioners from 90 % of NICUs (57 of 63 NICUs), 96 % of LNUs (80 of 83 LNUs) and 56 % of SCUs (37 of 66 SCUs) responded. Per annum, most NICUs and LNUs ventilated between 10 and 50 term-born infants, 42 % of NICUs ventilated more than 50 term-born infants, whereas 68 % of SCUs ventilated less than ten term-born infants (Fig. 1).

The three most frequently used ventilators for conventional ventilation, which is other than HFOV, were the SLE 5000, SLE 2000 (SLE Ltd., South Croydon, UK) and the Dräger Babylog 8000 or 8000plus (Dräger Medical, Lübeck, Germany); many units used more than one type of ventilator. HFOV was provided by all NICUs; several units used more than one type of oscillator: 49 % used the SLE 5000, 47 % the Sensormedics 3100A (CareFusion, San Diego, CA, USA) and 18 % the Stephanie (F. Stephan GmbH, Gackenbach, Germany).

It was reported that 26 % of NICUs and 11 % of LNUs used volume-targeted ventilation (VTV) routinely in term-born infants. A greater proportion of NICUs stated that they used VTV compared to LNUs as the initial ventilation mode, particularly for infants with RDS (p=0.0006) or congenital pneumonia (p=0.0005) (Table 1). A wide variety of volume-target levels (3–10 ml/kg) were stated to be used. In both NICUs and LNUs, the volume-targeted level was weaned before extubation to a median of 4 ml/kg, range 3–5 ml/kg. HFOV was stated to be used as the initial ventilation mode by a greater proportion of NICUs compared to LNUS and SCUs for meconium aspiration syndrome (p=0.044) or persistent pulmonary hypertension of the newborn (p=0.001) (Table 1). Conventional mechanical ventilation (CMV) was stated to be used as rescue mode by a greater proportion of LNUs compared to NICUs (p<0.001), whereas HFOV was stated to be used as rescue mode by a greater proportion of NICUs compared to LNUs (p<0.0001) (Table 2). The majority of SCUs stated that any infant requiring rescue support would be transferred to a unit providing a higher level of neonatal care. In 61 % of NICUs, infants were changed from HFOV to conventional ventilation prior to extubation, whereas in the other 39 % of units, infants were extubated directly from HFOV.

CPAP was used in a number of units, most commonly for infants with RDS (Table 1). For other respiratory conditions, CPAP was used more commonly in LNUs and SNUs. Pressure support ventilation was rarely used.

It was reported that surfactant was given in 61 % of units for infants with MAS and in 79 % of units for infants with RDS. The use of surfactant for different conditions did not differ significantly between different levels of care, except that surfactant was less likely to be given in SCUs than NICUs or LNUs for infants with RDS (p<0.0001) (Fig. 2). Too few of the LNUs or SCUs stated that they used nitric oxide to all meaningful analysis of their results. In 55 % of NICUs, nitric oxide was stated to be started at 20 ppm, in 25 % at 10 ppm and in 20 % at 5 ppm. In 76 % of NICUs, the maximum dose was stated to be 20 ppm, in 4 % 25 ppm and in 20 % 40 ppm.

Discussion

These results demonstrate that there was significant variation in respiratory support practices between hospitals providing different levels of neonatal care. This, in part, reflects that in line with the BAPM guidelines [3], SCUs and LNUs (to a lesser extent) transfer infants requiring

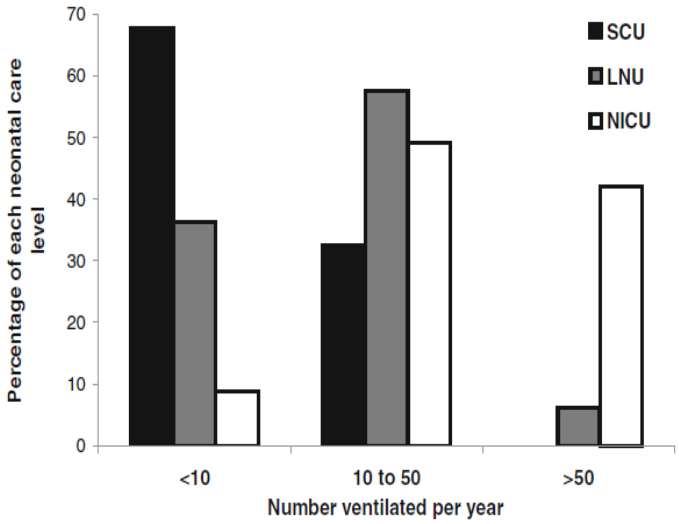

Fig. 1 Number of term-born infants per annum by level of neonatal care

rescue respiratory support to a unit providing a higher level of neonatal care. There were, however, variations in practice between NICUs, for example different levels of volume-targeting and different starting doses of iNO were used. There have been relatively few studies which have investigated respiratory support for term-born infants. The results of our survey also highlight that even where there is an evidence base, not all units have implemented such evidence (see the following discussion).

A recent survey of 173 European neonatal units highlighted that in a predominately prematurely born population, 85 % of patients were conventionally ventilated [19], whereas the results of another survey demonstrated that 60 % of Australasian NICUs and 40 % of Scandinavian NICUs routinely used VTV in prematurely born infants [11]. The latter survey's results perhaps reflect the positive benefits reported in prematurely born infants in the recent Cochrane Review [21]. We now demonstrate that 26 % of UK NICUs routinely use VTV in term-born infants, although there have been no randomised studies demonstrating similar benefits in term-born infants. Practitioners stated that they used volume-target levels from 3 to 10 ml/kg with the median minimum volume-target level used prior to extubation of 4 ml/kg. In term-born infants with acute respiratory distress, we have recently demonstrated that a VT level of 6 ml/kg rather than 4 ml/kg reduces the work of breathing [4].

A variety of ventilators were used for both conventional and high-frequency oscillatory ventilation. We have previously shown [17] that during VTV, different types of ventilators deliver different airway pressure waveforms, but whether this influences outcome has not been tested. Only 47 % of units stated that they used the Sensormedics for term-born infants. Oscillator performance also differs [12], with the Sensormedics delivering greater tidal volumes, particularly at lower frequencies compared to the Draeger and SLE ventilators in oscillator mode

For term-born infants, there is no evidence to support the use of prophylactic HFO and little evidence to support use of HFO in infants with severe pulmonary dysfunction born at or near term [9]. In a meta-analysis [9] of two randomised trials comparing HFOV to conventional ventilation (CV), no reductions in mortality at 28 days, pulmonary air leak, chronic lung disease (28 days or more in oxygen) or intracranial injury were demonstrated. In the one rescue study [5] included in the meta-analysis [9], there was no difference in the risk of needing extracorporeal membrane oxygenation (ECMO). Despite the paucity of evidence, the results of this survey demonstrated that many practitioners from NICUs indicated that they used HFOV as rescue mode. As their respiratory failure improves, infants on HFOV can be switched either to CMV for further weaning prior to extubation or be extubated directly from HFOV. There is no evidence to determine whether one method is better than the other for term-born infants, yet the majority of practitioners from NICUs stated that they changed infants to CMV from HFOV for a period prior to extubation.

There is evidence to support surfactant use in certain respiratory conditions in term-born infants. In meconium aspiration syndrome in infants born at or near term, a meta-analysis demonstrated that surfactant reduced the risk of requiring ECMO (relative risk (RR) 0.64, 95 % confidence interval (CI) 0.46, 0.91) [6]. A randomised, multicentre, double-blind, placebo-controlled trial in

Table 1 Initial mode of ventilation by diagnosis and level of neonatal care

		NICU (n=57)	LNU (n=80)	SCU (n=37)	p value
MAS	CPAP	2 (4 %)	19 (24 %)	10 (27 %)	0.002
	CMV	15 (26 %)	36 (45 %)	16 (43 %)	0.069
	SIMV	21 (37 %)	19 (24 %)	8 (22 %)	0.158
	ACV	14 (25 %)	5 (6 %)	3 (8 %)	0.004
	PS	0	0	0	NA
	Volume-targeted	8 (14 %)	6 (8 %)	0	0.049
	HFOV	3 (5 %)	0	0	0.044
RDS	CPAP	19 (33 %)	38 (48 %)	20 (54 %)	0.103
	CMV	8 (14 %)	17 (21 %)	9 (24 %)	0.409
	SIMV	17 (30 %)	23 (29 %)	5 (14 %)	0.153
	ACV	11 (19 %)	2 (3 %)	3 (8 %)	0.003
	PS	0	0	0	NA
	Volume-targeted	15 (26 %)	8 (10 %)	0	0.0006
	HFOV	0	0	0	NA
PPHN	CPAP	0	8 (10 %)	4 (11 %)	0.043
	CMV	17 (30 %)	42 (53 %)	24 (65 %)	0.002
	SIMV	17 (30 %)	18 (23 %)	7 (19 %)	0.433
	ACV	11 (19 %)	6 (8 %)	2 (5 %)	0.044
	PS	0	0	0	NA
	Volume-targeted	8 (14 %)	4 (5 %)	0	0.021
	HFOV	11 (19 %)	4 (5 %)	0	0.001
Congenital pneumonia	CPAP	8 (14 %)	24 (30 %)	16 (43 %)	0.007
	CMV	10 (18 %)	28 (35 %)	13 (35 %)	0.059
	SIMV	23 (40 %)	23 (29 %)	6 (16 %)	0.042
	ACV	13 (23 %)	3 (4 %)	2 (5 %)	0.0008
	PS	0	0	0	NA
	Volume-targeted	12 (21 %)	4 (5 %)	0	0.0005
	HFOV	0	0	0	NA
Non-respiratory, e.g. HIE	CPAP	3 (5 %)	18 (23 %)	6 (16 %)	0.023
	CMV	13 (23 %)	33 (41 %)	20 (54 %)	0.007
	SIMV	26 (46 %)	23 (29 %)	9 (24 %)	0.05
	ACV	10 (18 %)	5 (6 %)	2 (5 %)	0.054
	PS	2 (3.5 %)	0	0	NA
	Volume-targeted	10 (18 %)	4 (5 %)	0	0.004
	HFOV	0	0	0	NA

NA Not applicable

term infants with severe respiratory failure due to MAS, sepsis or idiopathic PPHN demonstrated that administration of surfactant was associated with a significant reduction in the need for ECMO (p=0.038), but no statistically significant difference in the duration of ventilation or the incidence of chronic lung disease [14]. A retrospective observational study [10] of 118 infants with respiratory failure and group B streptococcal infection, 19 % of whom were more than 35-week gestation, showed a significant reduction in the median fraction of inspired oxygen (FiO_2) with surfactant treatment (0.84 to 0.5, p<0.01). Observational studies, mostly in prematurely born infants with pulmonary haemorrhage, have shown that surfactant administration was associated with an improvement in the severity of respiratory failure [1] and a significant reduction in the mean oxygenation index [16]. No benefit, however, has been shown in administering surfactant to term-born infants with congenital diaphragmatic hernia (CDH). Indeed, in antenatally diagnosed, term-born, CDH patients, surfactant treatment was associated with a higher use of ECMO (p=0.04), a higher incidence of

Table 2 Rescue mode of ventilation by diagnosis and level of neonatal care

		NICU (n=57)	LNU (n=80)	p value
MAS	CMV	3 (5 %)	31 (39 %)	<0.0001
	SIMV	1 (2 %)	9 (11 %)	0.045
	ACV	1 (2 %)	11 (14 %)	0.015
	HFOV	50 (88 %)	27 (34 %)	<0.0001
RDS	CMV	3 (5 %)	36 (45 %)	<0.0001
	SIMV	6 (11 %)	9 (11 %)	1.000
	ACV	4 (7 %)	10 (13 %)	0.395
	HFOV	43 (75 %)	22 (28 %)	<0.0001
PPHN	CMV	4 (7 %)	27 (34 %)	0.0002
	SIMV	0	10 (13 %)	0.005
	ACV	1 (2 %)	7 (9 %)	0.139
	HFOV	51 (90 %)	30 (38 %)	<0.0001
Congenital pneumonia/aspiration	CMV	5 (9 %)	36 (45 %)	<0.0001
	SIMV	2 (4 %)	9 (11 %)	0.121
	ACV	3 (5 %)	10 (13 %)	0.237
	HFOV	44 (77 %)	20 (25 %)	<0.0001
Non-respiratory, e.g. HIE	CMV	9 (16 %)	42 (53 %)	<0.0001
	SIMV	1 (2 %)	11 (14 %)	0.015
	ACV	5 (9 %)	9 (11 %)	0.778
	HFOV	38 (67 %)	12 (15 %)	<0.0001

chronic lung disease (p=0.0066) and a lower survival rate (p=0.0033) [20].

Inhaled NO reduces the incidence of the combined outcome of death or need for ECMO in ventilated, term-born infants [7]. A review of four studies highlighted that the maximal beneficial effect of NO occurs at less than 30 ppm [15]; as a consequence, it has been recommended that the starting dose should be 20 ppm [7]. The results of this survey demonstrated that practitioners from only 55 % of NICUs stated that they were using a starting dose of 20 ppm [7].

A limitation of this study is that we approached a single practitioner from each of the units to complete the questionnaire. It may be that they responded with their personal views, but they were identified as the lead clinicians, and their views represent practitioners from different levels of neonatal care provision. Although practitioners from 90 % of NICUs and 96 % of LNUs responded to survey, the response rate from practitioners from SCUs was much lower (56 %). We do not, however, feel that this significantly affected our findings as

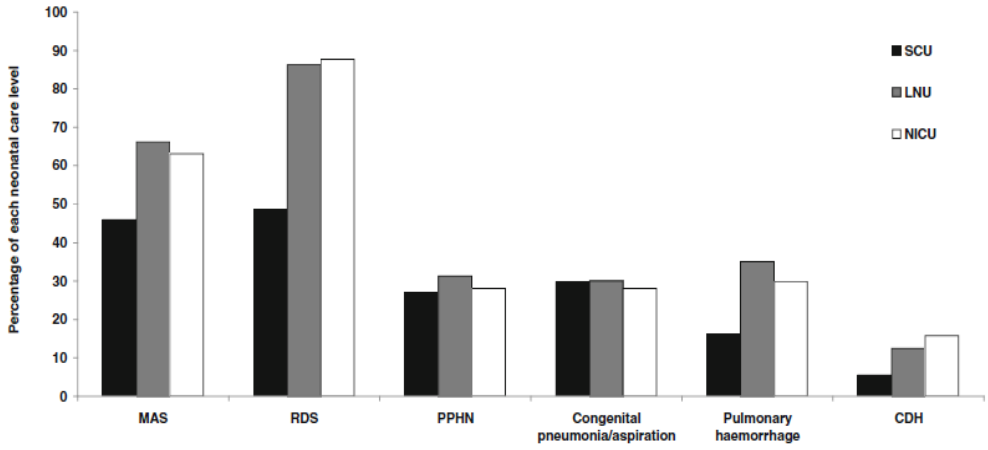

Fig. 2 Use of surfactant by diagnosis and level of neonatal care

SCUs provide only special care for their local population and should transfer infants with ongoing complex respiratory support requirements to NICUs [3]. Indeed, the majority of SCUs stated that any infant requiring rescue support would be transferred to a unit providing a higher level of neonatal care.

In conclusion, we have shown that there is considerable variation in respiratory support practice for term-born infants, particularly between practitioners from units offering different levels of neonatal care. These results emphasise that further research is required to produce evidence-based guidelines for the respiratory support of term-born infants.

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Volume-targeted ventilation in infants born at or near term

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ABSTRACT

Objectives To determine the impact of different volume-targeted (VT) levels during volume-targeted ventilation (VTV) on the work of breathing (WOB) of infants born at or near term and to investigate whether a level of VT reduced the WOB below that experienced on respiratory support without VT.

Design Prospective crossover study.

Patients Sixteen infants, median gestational age of 38 (range 34–41) weeks, birth weight of 3.1 (range 1.5–4.1) kg and postnatal age of 5 (range 2–17) days were studied. The infants were receiving time-cycled, pressure-limited ventilation in a continuous mandatory or in a triggered mode.

Interventions The infants were studied first without VT (baseline) and then at VT levels of 4, 5 and 6 ml/kg delivered in a random order. After each VT level, the infants were returned to baseline.

Main outcome measure The WOB was assessed by measuring the transdiaphragmatic pressure-time product (PTPdi).

Results One infant became apnoeic at VT of 6 ml/kg. At a VT level of 4 ml/kg, four infants were making such vigorous respiratory efforts that no inflations were delivered. The median PTPdi was higher at a VT level of 4 ml/kg than at 5 ml/kg ($p<0.01$) or 6 ml/kg ($p<0.001$). Only at a VT level of 6 ml/kg was the median PTPdi lower than that at baseline ($p<0.01$).

Conclusion Low VT levels (4 ml/kg) during VTV increase the WOB in ventilated infants born at term or near term. The results suggest that a VT level of 6 ml/kg could be used to reduce the WOB.

What is known on this topic

During weaning and acute respiratory distress, low levels of volume-targeted increased the WOB of prematurely born infants.

What this study adds

- Low levels of volume-targeted (VT) during volume -targeted ventilation increased the work of breathing (WOB) in infants born at or near term.
- Only a VT level of 6 ml/kg reduced the WOB below that experienced on ventilation without VT.

INTRODUCTION

During volume-targeted ventilation (VTV), a near constant tidal volume is delivered, even if rapid changes in the infant's lung function occur. The level of volume targeting (VT) influences the infant's work of breathing (WOB) as assessed by the measurement of the transdiaphragmatic pressure-time product (PTPdi).[1 2] Among the prematurely born infants with acute respiratory distress[1] or those studied during weaning,[2] a VT level of 6 ml/kg compared with 4 ml/kg was associated with a significantly lower PTPdi. Similar studies have not been undertaken including infants born at or near term. The aim, therefore, of this study was to determine in infants born at or near term, the impact of different levels of VT on the WOB.

PATIENTS AND METHODS

Infants ≥34 weeks in gestation at birth were eligible for inclusion if they were supported by a time-cycled, pressure-limited ventilator either in a continuous mandatory (CMV) or in a triggered mode (assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV)) and making spontaneous respiratory efforts. Infants with a congenital diaphragmatic hernia or a severe hypoxic-ischaemic encephalopathy (HIE) were excluded. The infants were entered into the study if their parents gave an informed written consent. The study was approved by the King's College Hospital Research Ethics Committee.

All the infants were ventilated using SLE 5000 ventilators (software version 4.3; SLE, South Croydon, UK). Throughout this study, a leak compensation level of 20% was used. Measurements were only carried out if the infant had blood gases in the normal range (pH 7.25 to 7.4, $PaCO_2$ 4.5 to 6.5 kPa). The WOB was measured first on baseline ventilation, that is, without VT and then measured during each of three 20-min periods of VTV with VT levels of 4, 5 and 6 ml/kg delivered in a random order. In between each period of VTV, the infants were returned to 'baseline' ventilation for 20 min and the WOB was again measured during each baseline period.

The WOB was assessed by the measurement of the transdiaphragmatic PTPdi. To measure PTPdi, oesophageal and gastric pressures were measured using a dual pressure transducer tipped catheter (Gaeltec, Dunvegan, Scotland). The air flow was measured using a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (±2 cm H_2O; MP45; Validyne, Northridge, California,

Table 1 Pressure-time product (cm H_2O s/min) related to volume-targeted levels. The results are displayed as median (range)

	Baseline	4 ml/kg	5 ml/kg	6 ml/kg
Overall (n=15)	256 (133–419)	310 (194–487)	232 (110–433)	163 (54–377)
CMV (n=4)	229 (159–354)	332 (260–487)	177 (129–312)	157 (116–186)
SIMV (n=8)	256 (133–419)	289 (194–428)	242 (131–433)	200 (54–377)
ACV (n=3)	285 (156–355)	319 (216–478)	138 (110–252)	128 (117–252)

ACV, assist control ventilation; CMV, continuous mandatory ventilation; SIMV, synchronous intermittent mandatory ventilation.

USA). The pneumotachograph was inserted between the endotracheal tube and the ventilator manifold. The tidal volume was obtained by the digital integration of the flow signal by the acquisition software. The expired tidal volume (VTe) was recorded to minimise errors resulting from the leaks around the endotracheal tube; the leaks would be greater during positive pressure inflation. Airway pressure was measured from a port on the side of the pneumotachograph using a differential pressure transducer (±100 cm H_2O; MP45; Validyne). Transdiaphragmatic pressure was calculated by the digital subtraction of the oesophageal from the gastric pressure using the acquisition software. PTPdi was calculated by the integration of the transdiaphragmatic pressure signal with time for each breath and expressed per minute. The beginning and the end of the inspiratory phase of each breath were determined from the phase transition of the flow signal. The mean PTPdi was calculated from 20 consecutive breaths during the last 5 min at the baselines and each VT level. The 'baseline' PTPdi was calculated by averaging the PTPdi at the four baseline periods. The mean VTe was determined from the 20 breaths used in the calculation of PTPdi. The mean peak inflating pressure (PIP) and infant's respiratory rate were recorded over the last 5 min at each VT level and at the baselines, and the total expiratory minute volume (infant plus ventilator) was calculated.

Analysis

Differences were assessed for statistical significance using Friedman's test with Dunn's multiple comparison test. GraphPad Prism 5 (GraphPad, La Jolla, California, USA) was used.

Sample size

Recruitment of 16 infants allowed the detection of a difference in the PTPdi results of 80 cm H_2O.s/min, with 80% power at the 5% level, which was the difference in the PTPdi results between the VT levels of 4 and 6 ml/kg seen in a study of prematurely born infants.[2]

Patients

Sixteen infants with a median gestation at birth of 38 (range 34–41) weeks and a birth weight of 3.1 (range 1.5–4.1) kg were studied at a median postnatal age of 5 (range 2–17) days. Prior to the study, five infants were supported by CMV, eight by SIMV and three by ACV. Two infants had a diagnosis of meconium aspiration syndrome, two persistent pulmonary hypertension of the newborn, two respiratory distress syndrome, nine infants had surgical conditions (five gastroschisis, two exomphalos major, two bowel obstruction) and one infant had moderate perinatal asphyxia. At baseline, immediately prior to the start of the study, the infants were receiving a median PIP of 16 (range 14–21) cm H_2O, positive end expiratory pressure of 5 (range 4–5) cm H_2O, inflation time (Ti) of 0.4 (range 0.34–0.5) s and an inspired oxygen fraction (FiO_2) of 0.21 (range 0.21–0.3). Twelve infants were ventilated via shouldered endotracheal tubes which have minimal or no leak,[3] four infants, who were studied postoperatively, were ventilated via straight tubes. Ten infants were receiving an intravenous infusion of morphine between 5 and 10 µg/kg/h.

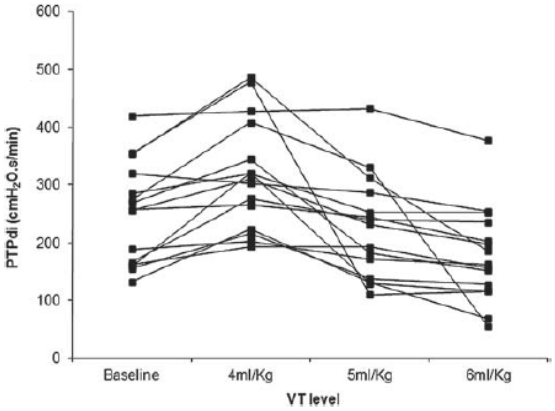

Figure 1 Pressure-time product results, the results at baseline are the average of the four baseline periods. Individual's results are shown as linked data points.

RESULTS

One infant with bowel obstruction was studied postoperatively and had a prolonged period of apnoea while receiving a VT level of 6 ml/kg. A capillary blood gas revealed a $PaCO_2$ of 4.0 kPa. Due to the lack of spontaneous respiratory effort, it was not possible to measure his PTPdi at a level of 6 ml/kg; hence, the infant's data were excluded from the analysis.

The mean PTPdi at a VT level of 4 ml/kg was higher than at 5 ml/kg ($p<0.01$) and 6 ml/kg ($p<0.001$) (table 1; figure 1). The mean PTPdi was only lower than at baseline at a VT level of 6 ml/kg ($p<0.01$). The mean PIP was significantly lower at a VT level of 4 ml/kg than at VT levels of 5 ml/kg ($p<0.05$) and 6 ml/kg ($p<0.001$) and at baseline ($p<0.001$) (table 2). The median VTe was significantly lower at a VT level of 4 ml/kg compared with that at VT levels of 5 ml/kg ($p<0.05$) and 6 ml/kg ($p<0.05$) and baseline ($p<0.05$). The inflation time was lower at a VT level of 4 ml/kg than at baseline ($p<0.05$). The infants' respiratory rates and the total minute volume did not differ significantly at baseline compared with any of the VT levels (table 2). The infants' median spontaneous VTe, however, was higher at 4 ml/kg than at baseline ($p<0.05$), 5 ml/kg ($p<0.01$) and 6 ml/kg (<0.05).

At a VT level of 4 ml/kg, four infants (three on triggered ventilation) on clinical observation were making vigorous respiratory efforts and our 'external' airway pressure recording demonstrated that they were receiving no ventilator inflations. The ventilator display, however, erroneously indicated that the infants were apparently receiving inflation pressures of between 7 and 9 cm H_2O. An in vitro study was carried out to examine this phenomenon further. A syringe was used to deliver the tidal volumes of 20 ml to the ventilator circuit with the VT level set at 10 ml and the recording system in place. This demonstrated that no positive pressure inflations were being delivered by the ventilator, but the ventilator recorded positive pressure changes in response to the 'expiratory' tidal volumes being delivered by the syringe.

Table 2 Peak inspiratory pressure, expiratory tidal volume, inflation time, infant spontaneous respiratory rate and expired tidal volume and total minute volume related to volume-targeted level. Results are displayed as median (range)

	Baseline	4 ml/kg	5 ml/kg	6 ml/kg
PIP (cm H_2O)	16 (14–21)	8 (0–14)	13 (7–20)	17 (8–21)
VTe (ml/kg)	6.4 (3.2–11)	5.0 (0–9.9)	5.8 (3–8.5)	6.5 (3.4–11.8)
Ti (s)	0.4 (0.34–0.5)	0.33 (0.25–0.4)	0.35 (0.27–0.4)	0.35 (0.27–0.4)
Infant respiratory rate (breaths/min)	65 (45–83)	66 (36–90)	60 (48–78)	60 (36–96)
Infant VTe (ml/kg)	4.0 (3.1–11.0)	5.8 (3.1–15.6)	4.1 (2.2–6.7)	4.1 (1.8–7.1)
Minute volume (ml/kg/ min)	326 (189–858)	339 (205–1030)	329 (198–608)	321 (209–726)

PIP, peak inflating pressure; Ti, inflation time; VTe, expired tidal volume.

DISCUSSION

We have demonstrated that the WOB, as assessed by measurement of PTPdi, in infants born at or near term was significantly higher at a VT level of 4 ml/kg compared with both VT levels of 5 and 6 ml/kg. Only a VT level of 6 ml/kg was associated with a significantly lower WOB compared with baseline. Prior to the study, the infants were receiving CMV or a triggered mode. The numbers on each ventilator mode were too small for subgroup statistical analysis but, although there was variability between individuals, there was a similar trend in the PTPdi levels with increasing VT levels for all three ventilator modes (table 1).

The infants were studied at VT levels within the tidal volume range, that is, 4 to 6 ml/kg. The infants required relatively low levels of ventilatory support as indicated by a maximum PIP of 21 cm H_2O, and thus were likely to have a mild respiratory disease. Thus, we did not use a VT level above 6 ml/kg, as, although that might have further reduced the WOB, it could have resulted in volutrauma or hypocarbia. Indeed, one infant had a prolonged period of apnoea at a VT level of 6 ml/kg and the $PaCO_2$ level was 4.0 kPa. Recent evidence[4] highlighted that in term-born infants with HIE, hypocarbia increased the risk of death or disability at 18 to 22 months. Thus, the present results suggest that a VT level of 6 ml/kg in at or near-term-born infants with mild respiratory distress should be used with careful monitoring.

The infants were ventilated using the SLE 5000, and the VTV mode with this ventilator terminates the inflation short of the preset inflation time if the inspiratory tidal volume exceeded the leak compensation setting. Throughout this study, a leak compensation of 20% was used. At a VT level of 4 ml/kg, certain infants received an inflation time of less than 0.3 s and the median inflation time was significantly shorter than at baseline. In addition, at a VT level of 4 ml/kg, four infants received no ventilator inflations; they were all making very vigorous efforts. The present in vitro study highlighted that 'expiratory' pressures generated in the circuit by the syringe were displayed by the ventilator as PIPs. Thus, the apparent PIPs displayed by the ventilator in the four infants with vigorous respiratory efforts were likely due to their active expiration.

Regardless of the VT level and despite the significantly lower PIP at a VT level of 4 and 5 ml/kg compared with 6 ml/kg, the minute volume did not differ significantly at any of the VT levels compared with baseline. The infants' respiratory rates also did not differ significantly between VT levels. Our results demonstrate that the infants compensated for the reduced support from the ventilator at lower VT levels by increasing the depth of their respiratory efforts and tidal volume exchange (table 2), and hence their WOB was increased at the lower VT level.

Infants with a variety of underlying diagnoses were included in the study, but they were representative of at or near-term-born babies who require ventilatory support. In addition, despite the heterogeneity of diagnoses, we saw significant differences in the results according to the VT level status. We feel our results are generalisable to this population, but further research is required to determine if the optimal VT would vary in term-born infants according to their underlying pathophysiology. Research is also required to deliver the optimal weaning strategy from VTV for term-born infants. In this study, the SLE 5000 was used. We have previously demonstrated that airway pressure waveform differs according to the type of ventilator used to deliver VTV.[5] Thus, it is possible that the results of the comparison of ventilation with and without VT might have been different if we had used a different ventilator type. We, however, used the same ventilator type to compare the different VT levels and ensured a minimum inflation time and have highlighted that lower VT compared with higher VT levels were associated with a greater WOB.

Optimising the tidal volume delivery is crucial to the success of mechanical ventilation, not least as it will be associated with the lowest WOB. We have highlighted that higher rather than lower levels of VT within the normal tidal volume range reduces the WOB in infants born at or near term, and this may be particularly important in acutely ill patients.

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Competing interests AG has held grants from various ventilator manufacturers and has received honoraria for giving lectures and advising various ventilator manufacturers. SH has received the sponsorship for postgraduate courses from ventilator manufacturers.

Ethics approval King's College Hospital Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Randomised Trial of Volume-Targeted Ventilation versus Pressure-Limited Ventilation in Acute Respiratory Failure in Prematurely Born Infants

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Key Words
Newborn · Volume-targeted ventilation · Pressure-limited ventilation

Abstract
Background: During volume-targeted ventilation (VTV), a constant volume is delivered with each ventilator inflation. ***Objectives:*** To determine whether VTV compared to pressure-limited ventilation (PLV) reduced the time to reach weaning criteria in prematurely born infants with acute respiratory distress, and if any difference was explained by better respiratory muscle strength and/or a lower work of breathing (WOB). ***Methods:*** Infants of <34 weeks of gestational age ventilated for <24 h in the first week after birth were randomised to receive either VTV or PLV. The primary outcome was the time to achieve pre-specified weaning criteria. Respiratory muscle strength was assessed by the measurement of the maximum inflation and expiratory pressures, and the WOB assessed by the transdiaphragmatic pressure time product. Other outcomes reported are the duration of ventilation, occurrence of patent ductus arteriosus, pneumothorax, intraventricular haemorrhage, periventricular leukomalacia and episodes of hypocarbia. ***Results:*** Forty infants, median gestational age 27 (range 23–33) weeks, were recruited. The time taken to achieve weaning criteria was similar in the two groups [median 14 h (VTV) vs. 23 h (PLV)]. There were no significant differences between the groups with regard to respiratory muscle strength, WOB or other outcomes, except that fewer of the VTV compared to the PLV group had episodes of hypocarbia (8 vs. 19; $p < 0.001$). ***Conclusion:*** In prematurely born infants with acute respiratory failure, use of VTV did not reduce the time to reach weaning criteria, but was associated with a reduction in episodes of hypocarbia.

Introduction

During volume-targeted ventilation (VTV), a relatively constant volume is delivered with each ventilator inflation regardless of changes in the infant's lung function. Meta-analysis of the results of randomised trials has demonstrated that VTV compared to pressure-limited ventilation (PLV) was associated with significant reductions in the combined outcome of death or BPD, pneumothorax and the combined outcome of periventricular leukomalacia (PVL) or grade III–IV intraventricular haemorrhage (IVH), and the duration of ventilation was significantly

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shorter in infants supported by VTV [1]. In the studies included in the meta-analysis [1], however, it is not possible to determine whether VTV compared to PLV was beneficial in the acute or weaning stages or both. Furthermore, different types of ventilators were used in the two arms of certain of the studies, which may have influenced the results. A wide range of reported tidal volume (VT) levels (4–10 ml/kg) were used in the studies included in the meta-analysis [1]. We have shown that in the short-term, the work of breathing (WOB) is reduced during VTV if higher rather than lower levels of volume targeting are used [2–4]. Increasing the level of respiratory support by increasing the level of volume targeting, however, could unfavourably impact on respiratory muscle strength. The aims, therefore, of this study were to determine in a randomised study of prematurely born infants with acute respiratory distress, whether VTV compared to PLV, using the same ventilator type, was associated with a shorter time to reach weaning criteria. We also wished to assess if any difference in the time to reach weaning criteria was associated with differences in the WOB or respiratory muscle strength between the two groups.

Methods

A randomised trial was carried out at King's College Hospital NHS Foundation Trust between August 2010 and February 2012. Infants born at <34 weeks of gestational age who were mechanically ventilated in the first week after birth were eligible for entry into the trial. Infants with major congenital anomalies, those who had been ventilated for more than 24 h and/or were supported by high-frequency oscillatory ventilation (HFOV) were ineligible. Infants were enrolled into the study if their parents gave informed written consent. The study was approved by King's College Hospital Research Ethics Committee.

Patients were randomised using sequential opaque sealed envelopes and random number table generation to receive either VTV or PLV. The infants in both arms of the trial were supported by SLE 5000 ventilators (Software versions 4.3; SLE Ltd., South Croydon, UK). The Unit's protocol was to use PLV during acute respiratory distress, that is inflation times of 0.3–0.4 s, rates of 40–60 bpm manipulated to try to achieve synchrony and peak pressures to achieve appropriate carbon dioxide levels ($PaCO_2$) (see later). The Unit's standard policy was for ventilated infants to receive intravenous morphine particularly if they were asynchronous. At randomisation, no changes were made to the ventilator settings of those infants who were to receive PLV. For those randomised to VTV, the only changes made were to set the VT level at 5 ml/kg with the leak compensation at 20% and a maximum peak inflation pressure (PIP) that allowed a delivery of 5 ml/kg. The maximum PIP was set at 5 cm H_2O above the PIP on the previous ventilation mode. If the VT was below 5 ml/kg on such settings, then the PIP was increased by 1–2 cm H_2O until the desired VT was reached. The SLE ventilator targets inflation volumes; all infants were ventilated via shouldered endotracheal tubes with minimal or non-existent leaks [5]. During VTV with an SLE 5000 ventilator, the maximum set peak inflation was delivered to the infant only if the VT level was not achieved. In addition, inflation is terminated once the VT level was achieved, which meant that the delivered inflation time might be shorter than the preset inflation time. Therefore, if the delivered inflation time was <0.2 s, the waveform was altered to give a shallower upstroke to the inflating pressure prolonging the inflation time. In this study, no such change was required. A VT of 5 ml/kg was used, as it had been shown in prematurely born infants to be associated with a lower WOB than a VT level of 4 ml/kg [3]. If infants developed a respiratory acidosis on VTV, the rate was increased in steps of 5–60 bpm, and then the VT level was increased in steps of 0.5 ml/kg to a maximum of 6 ml/kg with increases in the peak inflating pressure as necessary. If infants developed a respiratory acidosis on PLV, the rate was increased in steps of 5 bpm to a maximum of 60 bpm, and if necessary the pressure was increased. If those manoeuvres did not bring about the desired improvement in blood gases, the infant was transferred to HFOV. Infants were deemed to have failed the randomised mode if they required high frequency oscillation ventilation (HFOV) or a PIP >26 cm H_2O or had a pulmonary haemorrhage (diagnosed if there was fresh blood from the endotracheal tube associated with clinical deterioration which the attending clinician thought required the infant to receive muscle relaxation and/or a change to HFOV).

The primary end point was the time to reaching weaning criteria. Weaning criteria were defined in the PLV arm as the infant was receiving a PIP of ≤16 cm H_2O and an inspired oxygen concentration of ≤0.4, and additionally in the VTV arm that the infants were receiving a VT level of 5 ml/kg with the PIP ≤16 cm H_2O. Those settings had to have been maintained or weaned further over the subsequent 6-hour period. Once the infants reached weaning criteria, caffeine was administered. In the PLV arm, infants then followed the unit's routine practice, that is the infant was switched to assist control ventilation (ACV); synchronised intermittent mandatory ventilation (SIMV) was only used if the infant was hypocarbic on ACV despite reduction in pressures and not deemed ready for extubation. In the VTV arm, once the infants reached weaning criteria they were also switched to ACV/SIMV, but with the intention of volume targeting also being used. Throughout ventilation, the policy was to keep the $PaCO_2$ in the following ranges:

- 4.5–5.5 kPa on days 1–2 after birth
- 5–7 kPa on days 3–7 after birth
- with the arterial pH between 7.25 and 7.35
- after day 7, permissive hypercarbia was permitted providing the pH was above 7.25.

An episode of hypocarbia was defined as a $PaCO_2$ <4.5 kPa on any arterial blood gas measurement during the first 72 h after birth. The number of arterial blood gases obtained in that time period was recorded. All infants received intravenous morphine (5–20 μg/kg/h) if they were asynchronous with the ventilator, and this was compromising oxygenation.

Measurements of the WOB and respiratory muscle strength were performed immediately prior to extubation. The WOB was assessed over a 5-min period by measurement of the transdiaphragmatic pressure time product (PTPdi) as previously described [3]. The PTP is related to the metabolic costs of breathing and correlates with the oxygen uptake of the respiratory muscles. PTPdi

therefore provides an estimate of the WOB performed by the diaphragm [6]. The mean PTPdi was calculated from the first set of 20 consecutive breaths which were without artefact and included both supported and unsupported breaths. Respiratory muscle strength was assessed by measuring the maximum inflation (Pi_{max}) and maximum expiratory pressure (Pe_{max}) generated during an airway occlusion during crying as previously described [7]. The clinicians caring for the infants were blinded to the results of the physiological measurements.

The nurses recorded the level of respiratory support hourly on observation charts. The infants' demographics and respiratory support levels at randomisation and pre-extubation were determined from the medical records and intensive care observation charts. The duration of ventilation was the time from randomisation to successful extubation (the infant remained extubated for at least 48 h). The indications for reintubation were the development of a respiratory acidosis (pH <7.25) which persisted for more than 4 h, the occurrence of frequent apnoeas or one major apnoea and/or an increased oxygen requirement (FiO_2 >0.6).

Sample Size

Using results from prematurely born infants previously ventilated on the unit, we calculated that recruitment of 40 infants allowed detection of a difference between the groups in the time to achieve weaning criteria of 72 h with 90% power at the 5% level. That sample size allowed us to detect a difference in the results of the physiological measurements equivalent to one standard deviation with 80% power at the 5% level.

Analysis

The analysis was conducted on an intention to treat basis. Outcome data were analysed using Cox regression as there was censoring of the primary outcome. Results are given as hazard ratios with 95% confidence intervals. In addition, the Cox model was used to estimate the median time to weaning by ventilation group. An imbalance was observed in baseline characteristics for birthweight, gestation and antenatal steroid use. Principal component analysis was used to reduce those three variables to two to facilitate stable adjustment in the Cox model. Hence, the primary outcome analysis was adjusted for the imbalance, and adjusted median weaning times were calculated from the Cox model as a sensitivity analysis. The results of the physiological measurements were slightly skewed, which was not corrected by transformation; hence, they were analysed using t tests, but as a sensitivity analysis tests were also done using the Mann-Whitney U test. Binary outcomes were analysed using χ^2 or Fisher's exact tests as appropriate. All analyses were conducted using Stata v11.

Results

There were 93 eligible infants during the study period (fig. 1). The recruited infants were of a lower gestational age than the non-recruited infants (median 27, range 23–34 weeks, vs. 29, range 24–34 weeks, respectively; p = 0.022) and were of lower birthweight (median 916, range 500–2,122 g, vs. 1,190, range 545–2,526 g, respectively; p = 0.0138). Despite randomisation, there was imbalance with regard to birthweight, gestational age and antenatal steroid use (table 1). Twelve infants in the VTV arm and 16 in the PTV arm received intravenous morphine. When the infants reached weaning criteria, i.e. those who had not met failure criteria, the 15 infants on VTV were switched to ACV with volume targeting and 17 infants on PLV were switched to ACV. The ventilator settings immediately after randomisation were similar in the two groups (table 1). In only 2 infants (birthweight 918 and 1,080 g, respectively) was it necessary to increase the VT level above 5 ml/kg because of respiratory acidosis.

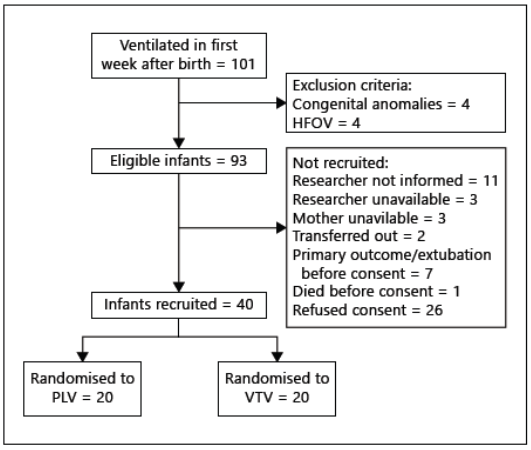

Fig. 1. Consort diagram of recruitment.

Table 1. Demographics by ventilation mode

	PLV (n = 20)	VTV (n = 20)
Gestational age, weeks	26 (24–33)	28 (23–33)
Birthweight, g	856 (570–2,122)	1,016 (550–2,120)
Males	11 (55)	10 (50)
Completed course of antenatal steroids	11 (55)	14 (70)
Immediately after randomisation		
Age, h	4 (0.3–10.0)	5 (1–21)
PIP, cm H_2O	20 (17–23)	20 (16–24)
Inflation time, s	0.37 (0.34–0.4)	0.36 (0.34–0.4)
FiO_2	0.31 (0.21–0.62)	0.33 (0.21–0.70)

Data are presented as median (range) or n (%).

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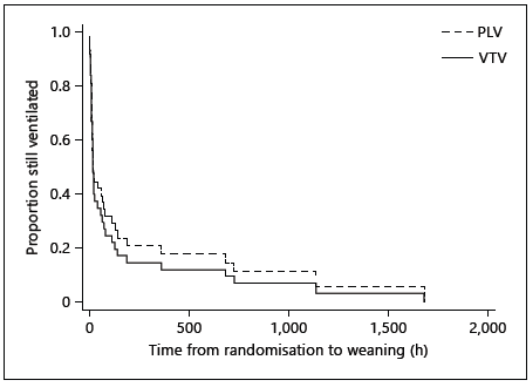

Fig. 2. Kaplan-Meier curve for the time to randomisation to meet weaning criteria.

There were no significant differences in the time either to achieve weaning criteria [median 14 h (VTV) vs. 23 h (PLV), hazard ratio = 0.77 (95% confidence interval: 0.40–1.48, p = 0.43); fig. 2] or successful extubation or the number of infants in each group who met failure criteria (table 2). After adjusting for baseline imbalance, the difference in the time to achieve weaning criteria between the groups was reduced [median 18 h (VTV) vs. 20 h (PLV), hazard ratio = 0.49, 1.87]. The ventilator settings at extubation were similar in the two groups (table 2).

There were no significant differences between the two groups in the median PTP, Pi_{max} or Pe_{max} results (table 3). The only significant difference in other outcomes was that fewer infants in the VTV compared to the PLV arm had episodes of hypocarbia (8 vs. 19, p < 0.001; table 4). The number of blood gases obtained in the first 72 h after birth was similar in each group (table 4).

Discussion

We have demonstrated no statistically significant difference in the time to reach weaning criteria in prematurely born infants with acute respiratory distress supported by PLV or VTV; indeed, the adjusted median times differed by 2 h. Our sample size allowed detection of a difference in the time to reach weaning criteria of 72 h, but unexpectedly the majority of infants in both groups met the criteria within 72 h. Our sample size, however, was also powered to detect a difference in the results of the physiological measurements equivalent to one

Table 2. Outcomes by mode of ventilation

	PLV	VTV	p value
Time to achieving weaning criteria, h	23 (6–1,679)	14 (1–1,138)	0.43
After adjusting for baseline imbalance, h	18	20	0.49
Met failure criteria	3	5	0.69
Causes			
Required HFOV	3	3	
Had a pulmonary haemorrhage	0	2	
Failed first extubation	6	3	0.45
Duration of ventilation, h	114 (6–1,696)	49 (1–1,206)	0.18
At extubation			
PIP, cm H_2O	15 (9–16)	14 (6–17)	0.38
Inflation time, s	0.35 (0.32–0.38)	0.36 (0.34–0.38)	0.20
FiO_2	0.24 (0.21–0.42)	0.23 (0.21–0.40)	0.83

Data are presented as median (range) or n.

Table 3. Results of the physiological measurements before extubation by ventilation mode

	PLV	VTV	p value
PTP, $H_2O \cdot s/min$	162.30 (77–295), 8	205.80 (74–225), 7	0.61
Pi_{max}, cm H_2O	38.1 (5.7–64.9), 11	38.9 (15.6–58.0), 8	0.97
Pe_{max}, cm H_2O	14.5 (7.4–35.4), 10	17.7 (4.2–45.6), 8	0.89

Data are presented as median (range) and the number of infants for whom results were available.

Table 4. Other outcomes

	PLV	VTV	p value
In the first 72 h			
Episodes of hypocarbia	19	8	<0.001
Episodes of hypocarbia/patient	3 (0–13)	0 (0–8)	0.0013
Number of blood gases	17 (5–29)	16 (4–30)	0.5515
PDA treated with ibuprofen	7	2	0.13
PDA ligation	2	1	1.00
Pneumothorax	0	2	0.23
IVH ≥grade 3	3	0	0.23
Cystic PVL	0	1	1.00
Postnatal steroids	2	2	1.00
Oxygen dependency at 28 days	14	11	0.30

Data are presented as the number of infants affected or median (range). PDA = Patent ductus arteriosus.

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standard deviation, and we demonstrated no significant differences in the pre-extubation WOB or respiratory muscle strength results. Those measurements were made when the infants in the PLV arm had been transferred to ACV for weaning from ventilatory support, but the infants in the VTV arm remained additionally on volume targeting. Our results then reflect that a combination of PLV and ACV was associated with similar levels of WOB and respiratory muscle strength as a combination of VTV and ACV with volume targeting. Our data suggest that VTV as used in this study and PLV provided similar levels of respiratory support to prematurely born infants with acute respiratory distress. Indeed, immediately after randomisation, the PIP and inflation times did not differ between the two groups.

The duration of ventilation tended to be longer in the PLV group; that difference did not reach statistical significance, and our study was not powered to test that outcome. Other secondary outcomes of patent ductus arteriosus, pneumothorax, IVH grade ≥3, cystic PVL and BPD are reported only to give the reader more information regarding the population we studied. The episodes of hypocarbia did differ significantly between the two groups. This seems unlikely to be by chance given the level of significance and the limited number of secondary outcomes. In addition, the number of blood gases obtained during the first 72 h did not differ significantly between the two groups. The finding confirms that reported in the Cochrane review [1] and is important as hypocarbia in prematurely born infants is significantly associated with the development of PLV and adverse neurodevelopmental outcomes [8].

Our study has a number of strengths and some limitations. The same ventilator type was used in both arms of the study as performance differs according to type of ventilator with regard to airway pressure waveforms [9]. We recruited consecutive infants who fulfilled the eligibility criteria and a researcher was available. The recruited infants, however, were significantly less mature and of lower birthweight than those not recruited; thus, we emphasise our results apply to very prematurely born infants. A criterion for failure of the randomised mode was a peak inflating pressure >26 cm H_2O; interestingly, no infant met that criterion. In the PLV arm, rate manipulation had been used to synchronise the infant's respiratory efforts with mechanical ventilation. Infants in each arm received intravenous morphine, which may have reduced their spontaneous respiratory efforts. Similar numbers of infants in each of the randomised arms received intravenous morphine; thus, it seems unlikely this influenced the results. Caffeine was given when the infants reached weaning criteria; some units start caffeine on the first day after birth. As a consistent approach was used to all infants in the trial, our use of caffeine is unlikely to have affected the results. The clinicians were not blinded to the intervention and indeed were not in any of the studies included in the meta-analysis [1]. The lack of significant differences in most of our results would suggest that the lack of blinding had not influenced performance of the study.

In conclusion, in prematurely born infants with acute respiratory distress, VTV compared to PLV as implemented using the SLE ventilator did not improve the time to reach weaning criteria or the results of physiological assessments. The significant reduction in episodes of hypocarbia in the VTV versus the PLV group suggests that VTV might improve long-term outcome. That hypothesis needs to be assessed in an appropriately sized randomised controlled trial.

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